Synthesis and stereochemistry of some isoquinoline alkaloids and related compounds.

Warren, Paul

Award date:
1978

Awarding institution:
University of Bath

SYNTHESIS AND STEREOCHEMISTRY OF SOME ISOQUINOLINE ALKALOIDS AND RELATED COMPOUNDS

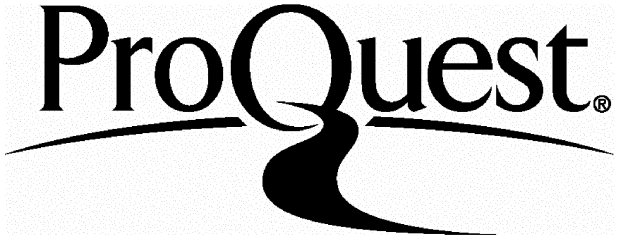
submitted by Paul Warren

for the degree of PhD

of the University of Bath

1978

P Warren



CONTENTS

ACKNOWLEDGEMENTS

I would like to thank my supervisor Dr. S. F. Dyke for his advice and encouragement during the course of this work. I would also like to thank Mrs. S. Briody for excellent laboratory facilities, Mr. D. Woods for nmr spectra and Mr. R. Brown for mass spectra. Finally, I would like to thank my wife Susan for the many hours of hard work she put into the typing of this thesis.

SUMMARY

This thesis describes work carried out by the author between October 1975 and October 1978. The first chapter describes a successful attempt to rigorously prove the absolute stereochemistry of the isopavinane alkaloids by synthesis of an optically active member of this group from an intermediate of known absolute configuration.

The second chapter briefly reviews the phenethylisoquinoline alkaloids and describes the synthesis of novel phenethylisoquinoline derivatives which are homologues of the isopavinane alkaloids. Although these "homoisopavinanes" have not been found to occur naturally to date, it is the author's belief that they represent a highly probable alkaloid class.

Intramolecular oxidative aryl-aryl coupling of phenolic and non-phenolic substrates plays an important role in the biosynthesis and synthesis of a number of alkaloids and other polycyclic compounds. Recently a number of reports describing the use of vanadium oxytrifluoride as an efficient reagent for effecting such oxidative couplings have appeared. For several years, workers in this laboratory have been trying to devise an efficient synthetic route to isomers of the aporphine alkaloids based on the dibenz [de,g] isoquinoline system. The final chapter of this thesis briefly reviews oxidative coupling with particular emphasis on the use of vanadium oxytrifluoride and describes the successful application of this reaction to the synthesis of two isomers of the aporphines based

on the dibenz [de,g] isoquinoline system. Attempts to isolate a postulated intermediate in these reactions are also described. Finally, the successful application of this oxidative coupling reaction to the synthesis of a 9-aminophenanthrene derivative is described.

CHAPTER 1

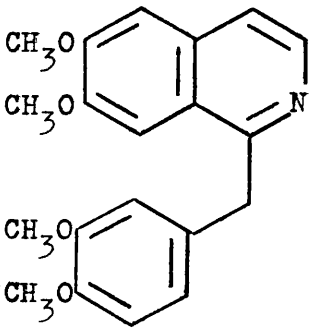
PAVINANE AND ISOPAVINANE ALKALOIDS
CORRELATION OF ABSOLUTE CONFIGURATIONS
BY SYNTHESIS

INTRODUCTION

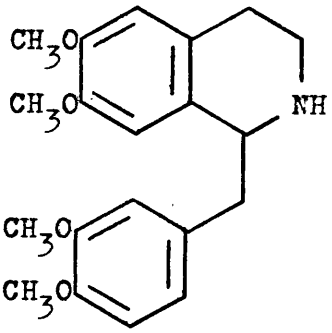
Historical Background

Reduction of papaverine (1) with tin and hydrochloric acid affords, in addition to the expected tetrahydropapaverine (2), a second base pavine[1] in 5% yield.

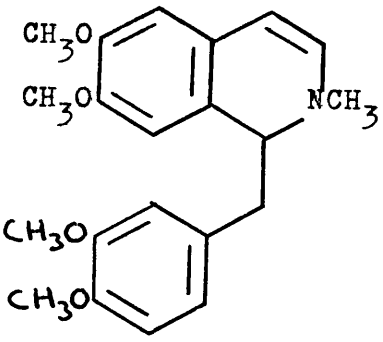
Schopf found that N-methylpavine is formed when N-methyl-1, 2-dihydropapaverine (3) is treated with acids and proposed structures (4) or (5) for pavine[2].



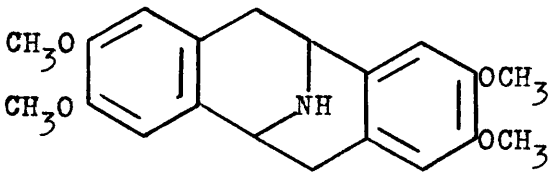
(1)



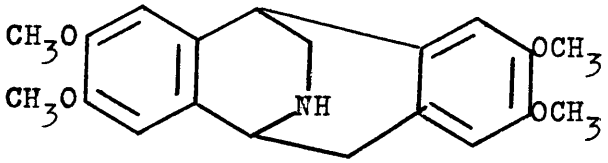
(2)



(3)

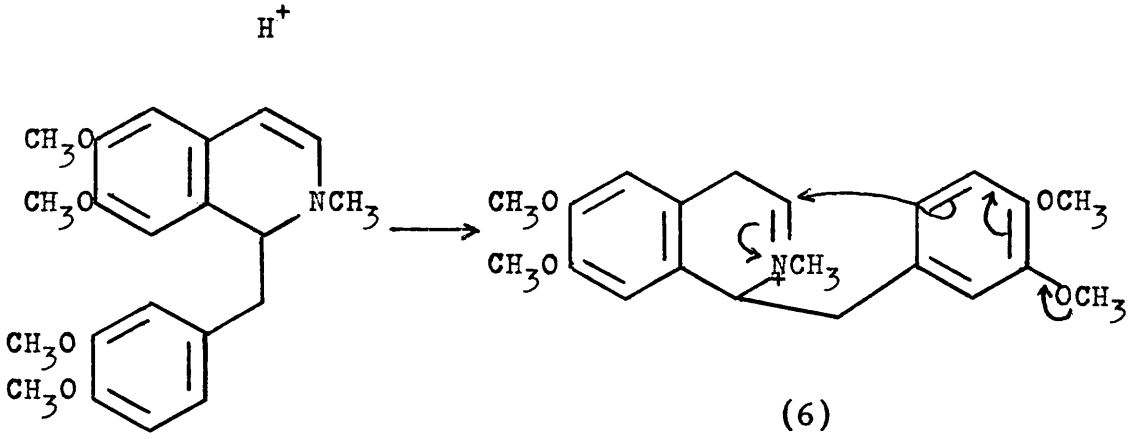


(4)



(5)

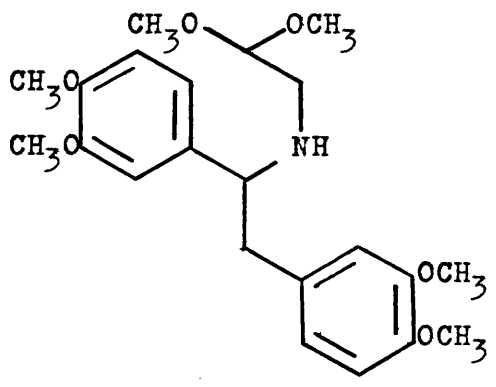
Battersby and Binks[3] established the structure of pavine as (4), by synthesis of its Hofmann degradation product and rationalised the formation of N-methylpavine reported by Schopf, as the intramolecular nucleophilic substitution of the protonated enamine (6) (Scheme 1). The isomeric base (5) was given the trivial name isopavine by Battersby and Yeowell, who showed[4] it to be the main product obtained when the benzylaminoacetal (7) was treated with mineral acid.



(6)

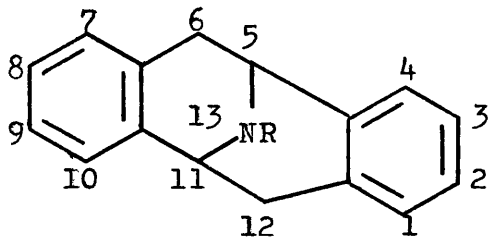
Scheme 1

N - methyl pavine

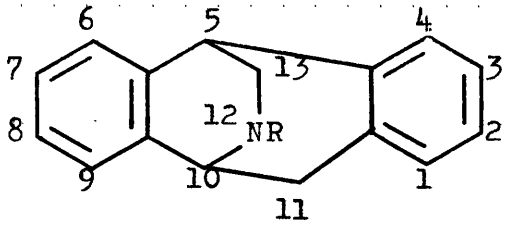


(7)

Compounds based on the parent ring systems of pavine and isopavine are known as pavinanes and isopavinanes respectively. The pavinane ring system (8) and isopavinane ring system (9) are numbered as shown.



(8)



(9)

The Alkaloids and their Occurrence

Alkaloids based on both the pavinane (8) and the isopavinane (9) ring systems are known[5]. Most of the naturally occurring compounds have R = methyl, although recently, quaternary methyl salts based on both systems have been isolated from natural sources. The alkaloids within a given series usually differ from one another only in the nature and position of oxygen functions attached to the aromatic rings. The structures of the known pavinanes and isopavinanes are summarised in Tables I and II respectively and Table III shows some of the other groups of isoquinoline alkaloids which have been isolated within genera producing pavinanes and isopavinanes.

Compound	Substituent on C or N atom 2	3	4	8	9	13	m.p. °C	$[\alpha]_D^a$
Argemonine	OCH_3	OCH_3	H	OCH_3	OCH_3	CH_3	155	-188(C)
Norargemonine	OCH_3	OCH_3	H	OCH_3	OH	CH_3	238	-154(C)
Isonorargemonine[c]	OCH_3	OCH_3	H	OH	OCH_3	CH_3	177	
Bisnorargemonine							254	-266(M)
Rotundine							245	-266(M)
Eschscholtzine	$O-CH_2-O$		H	$O-CH_2-O$		CH_3	128	-202(M)
Californidine	$O-CH_2-O$		H	$O-CH_2-O$		$(CH_3)_2^+$	286	-212[b]
							326	-217
Eschscholtzidine	$O-CH_2-O$		H	OCH_3	OCH_3	CH_3	oil	-194(M)
Caryachine	$O-CH_2-O$		H	OH	OCH_3	CH_3	175	-270(M)
Isocaryachine[c]	$O-CH_2-O$		H	OCH_3	OH	CH_3	206	
Munitagine							169	-239(C)
O,O-dimethyl -munitagine	H	OCH_3	OCH_3	OCH_3	OCH_3	CH_3	125	-292(C)
Platycerine	H	OCH_3	OH	OCH_3	OCH_3	CH_3	132	-267(C)

TABLE I - PAVINANES

a) C = chloroform, M = methanol. b) iodide. c) not isolated from plant material.

Compound	Substituent on C or N atom 2	3	7	8	12	m.p. °C	$[\alpha]_D^a$
Amurensine	OH	OCH_3	$O-CH_2-O$		CH_3	215	-178(M)
Isoamurensine[c]	OCH_3	OH	$O-CH_2-O$		CH_3		
Amurensinine	OCH_3	OCH_3	$O-CH_2-O$		CH_3	164	-162(C)
Reframidine	$O-CH_2-O$		$O-CH_2-O$		CH_3	amorphous	-123(M)
Reframine	$O-CH_2-O$		OCH_3	OCH_3	CH_3	amorphous	-146(M)
Remrefine	$O-CH_2-O$		OCH_3	OCH_3	$(CH_3)_2^+$	242[b]	-147(W)
Reframoline	$O-CH_2-O$		OH	OCH_3	CH_3	amorphous	-140(M)
Isoreframoline[c]	$O-CH_2-O$		OCH_3	OH	CH_3	216	
Thalisopavine	OH	OCH_3	OCH_3	OCH_3	CH_3	211	-210
O-methyl-thalisopavine[c]	OCH_3	OCH_3	OCH_3	OCH_3	CH_3	166	
Isopavine[c]	OCH_3	OCH_3	OCH_3	OCH_3	H	149	

TABLE II - ISOPAVINANES

a) C, Chloroform; M, Methanol; W, Water

b) Chloride

c) Not isolated from plant material

	isopavine	pavine	proaporphine	aporphine	berberine	protopine	benzo [c] phenanthridine
argemone	-	+	-	-	+	+	+
cryptocarya	-	+	-	+	-	-	-
eschschaltzia	-	+	-	-	-	+	+
papaver	+	-	+	+	+	+	+
roemema	+	-	+	+	+	+	-
thatictrum	+	+	-	+	+	-	-

TABLE III

Structure Elucidation

The pavinane and isopavinane alkaloids are easily distinguished from other tetracyclic alkaloids such as aporphines, berberines and benzo [c]phenanthridines by modern instrumental techniques. However, pavinanes and isopavinanes are very similar in most aspects of their chemistry and differentiation between these two groups of alkaloids is based upon their differing Hofmann exhaustive methylation products and mass spectral behaviour.

a) Hofmann Exhaustive Methylation[6,7,8]

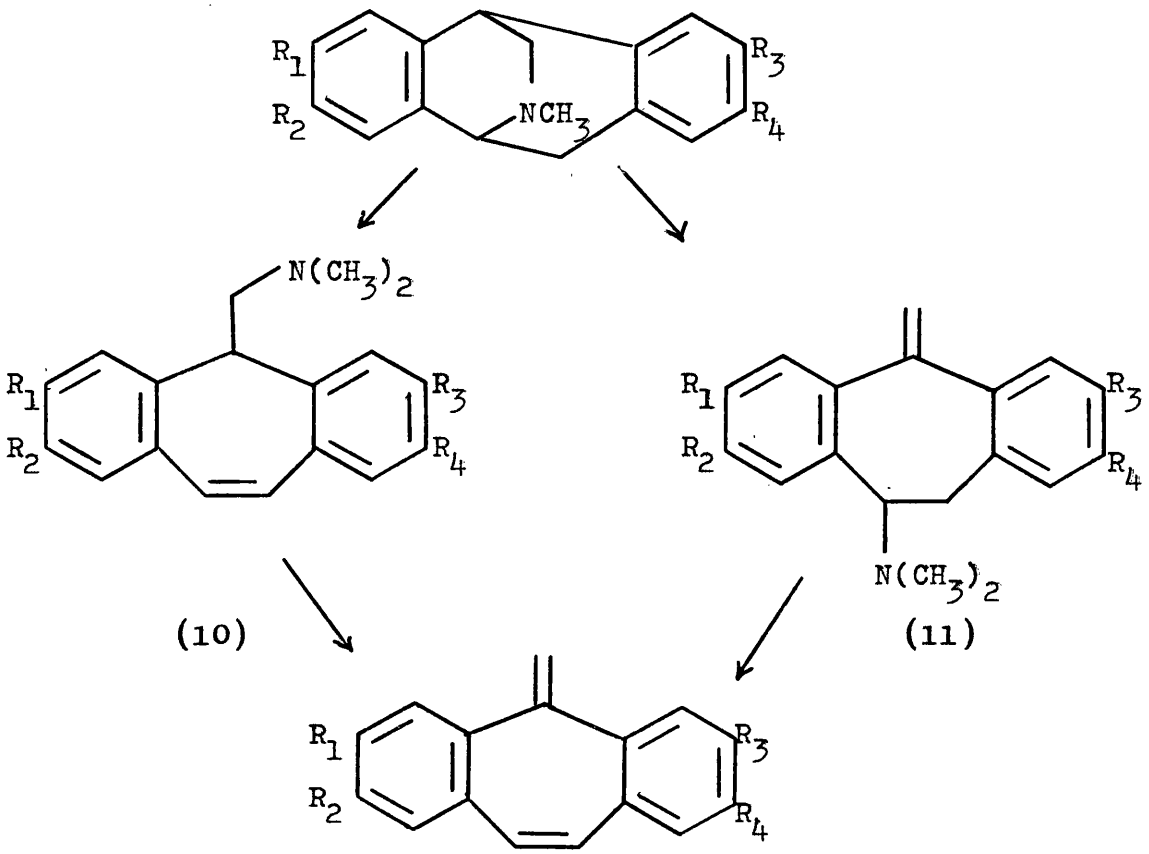
Of the two possible methine bases formed as products of the first step of the degradation of isopavinanes (Scheme 2) only those of type (10) are obtained in practice. The only exception is the alkaloid amurensinine which gives methines of both types (10) and (11)[9]. The second step affords the bismethine (12).

Both possible methines (13) and (14) are equally favoured as products of the first step of Hofmann exhaustive methylation of pavinanes, and a second step gives rise to a cyclooctatetraene derivative of the type (15).

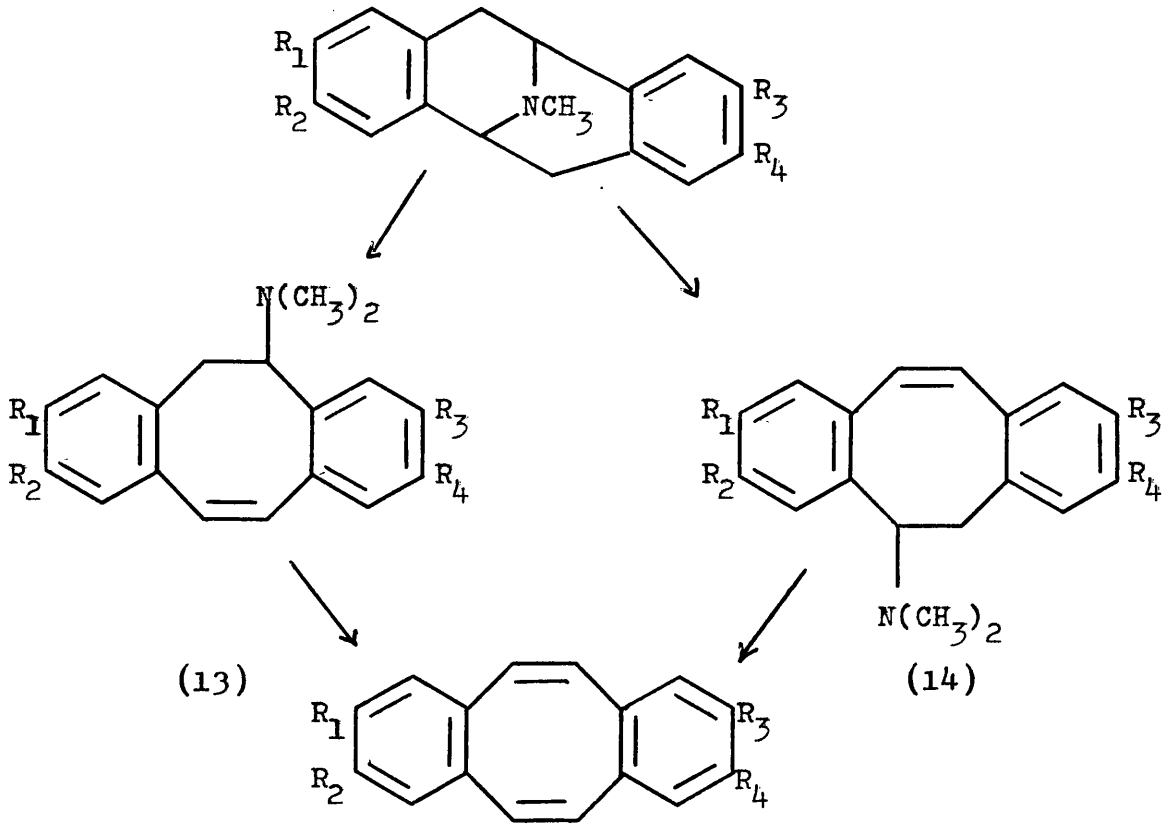
b) Mass Spectrometry (Scheme 3)[10,11]

In addition to a fairly strong molecular ion and (M-1) peak, the mass spectra of isopavinanes are characterised by the presence of a fairly strong peak due to the fragment (a) arising from a retro Diels-Alder loss of the nitrogen bridge. The base peak of the spectrum is provided by the isoquinolyl fragment (b).

The mass spectra of pavinanes again show a fairly strong

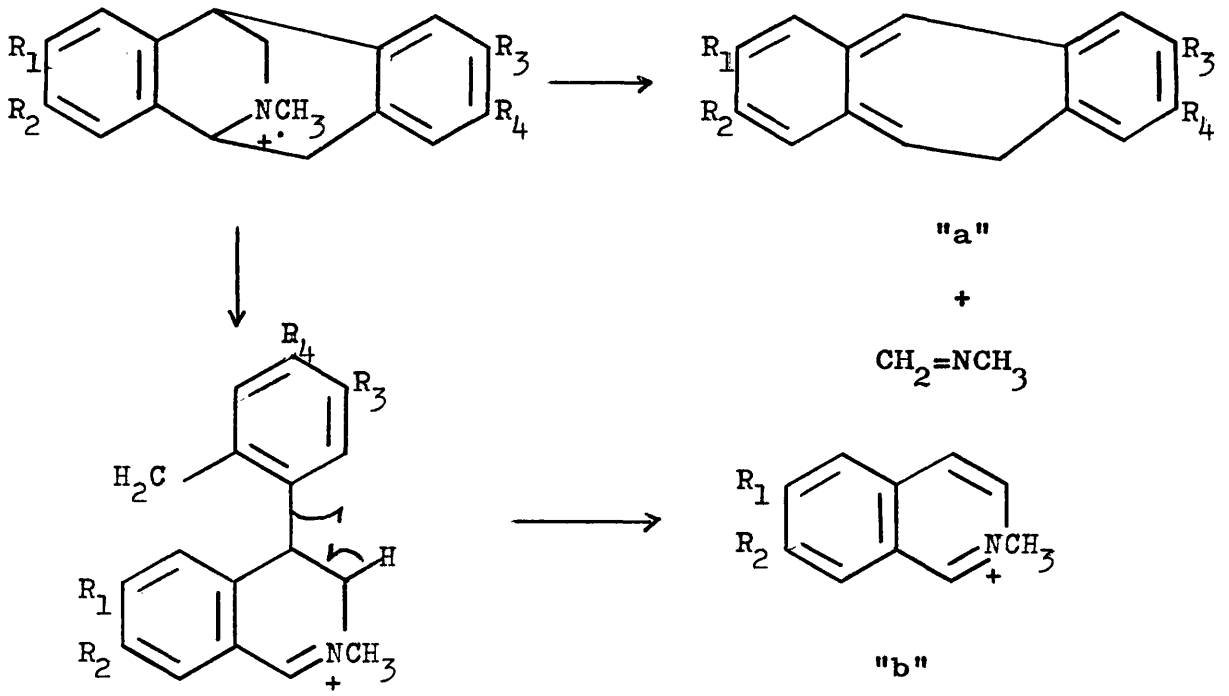


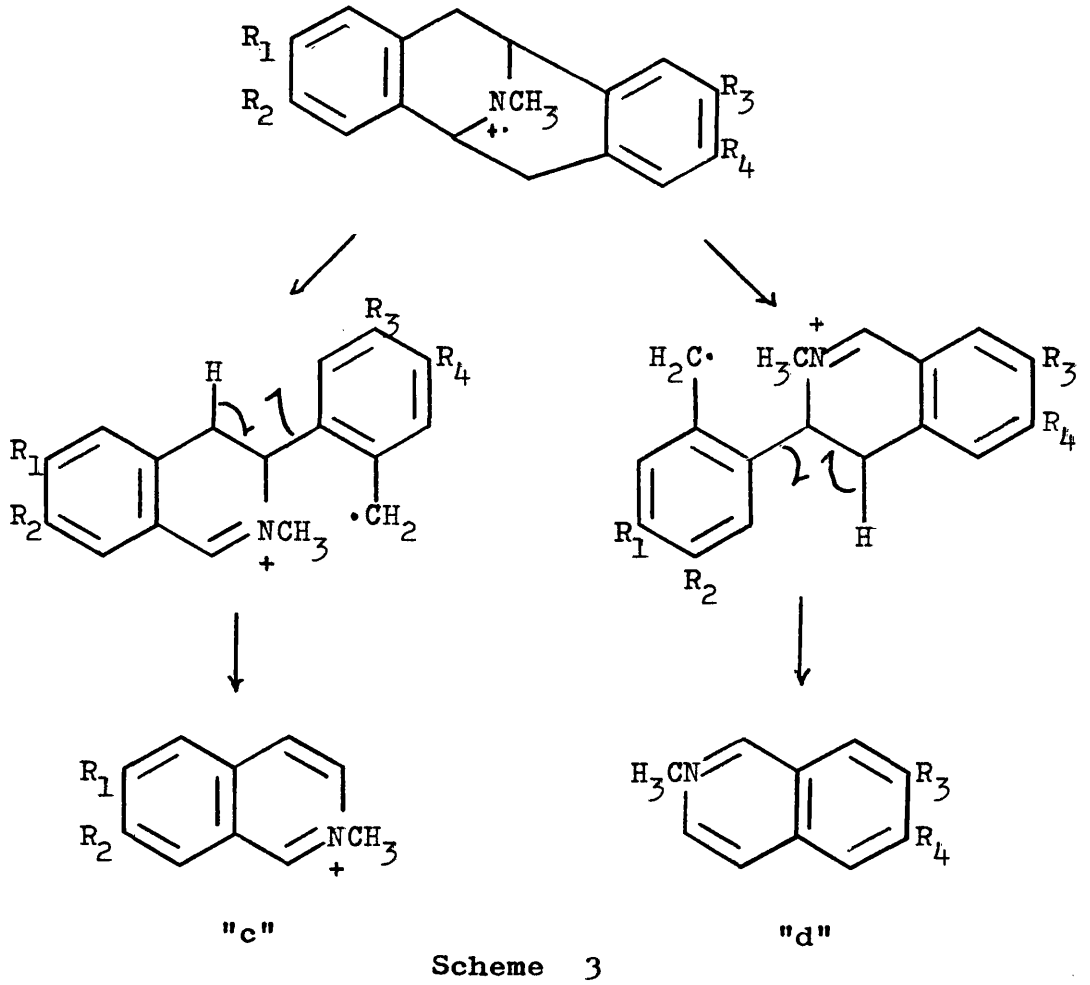
(12)



(15)

Scheme 2





Scheme 3

molecular ion and (M-1) peak, but do not show a retro Diels-Alder fragmentation due to the fact that the structure is branched at both carbons α to the nitrogen. The spectra of pavinanes are characterised by the presence of two strong peaks of almost equal intensity due to the two possible isoquinolyl fragments (c) and (d), one of which forms the base peak of the spectrum.

c) Nuclear Magnetic Resonance

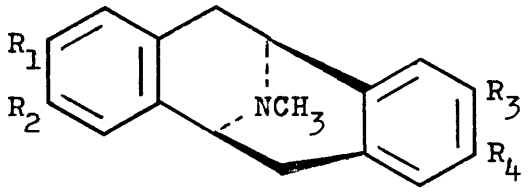
Chen and Soine have advanced additivity rules to predict chemical shifts of aromatic protons of pavinanes for spectra recorded in DMSO[12]. In 2,3,8,9 tetrasubstituted pavinanes the protons at positions 4 and 10 resonate at lower field than those at positions 1 and 7. Chen and Soine attributed this to deshielding of the former protons by the inductive effect of the nitrogen bridge. However, it seems more likely that anisotropic shielding rather than deshielding is responsible for this observation[13], as examination of molecular models shows that shielding by the aromatic rings is such that H_1 and H_7 are more shielded than H_4 and H_{10}.

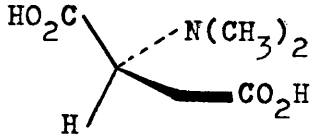
In view of the unsymmetrical nature of the isopavinane ring system it is not surprising that a set of empirical rules for predicting chemical shifts, similar to those for pavinanes could not be found. No firm assignments could be made for the aromatic proton absorptions which in most cases appear as three or four singlets.

Stereochemistry

The absolute stereochemistry of the pavinane alkaloid (-) argemonine (16a) was conclusively proved by Barker and

Battersby[14], by degradation to (-) N,N-dimethylaspartic acid (17) of known absolute configuration. This assignment was supported by a non empirical analysis of the circular dichroism (c.d.) spectrum[15] and an empirical optical rotatory dispersion (o.r.d.) study[16]. This allowed assignment of absolute configuration to be made for (-) norargemonine (16b), (-) bisnorargemonine (16c), (-) eschscholtzine (16d), (-) caryachine (16e) and (-) eschscholtzidine (16f), since all had been correlated chemically with (-) argemonine[17-19].



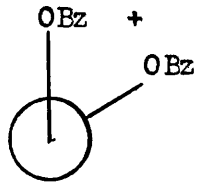


(17)

	R_1	R_2	R_3	R_4
(16a)	OCH_3	OCH_3	OCH_3	OCH_3
(16b)	OCH_3	OH	OCH_3	OCH_3
(16c)	OCH_3	OH	OCH_3	OH
(16d)	$O\text{-}CH_2\text{-}O$		$O\text{-}CH_2\text{-}O$	
(16e)	OH	OCH_3	$O\text{-}CH_2\text{-}O$	
(16f)	$O\text{-}CH_2\text{-}O$		OCH_3	OCH_3

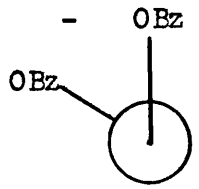
In a skilful exploitation of the chiroptical properties of coupled chromophores, Nakanishi[20] showed that a simple relationship existed between the chirality of α-glycol dibenzoates and the sign of the longer-wavelength component of the bisignate c.d. curve centred near 255 nm, which was

associated with coupling of the π-π^* intramolecular charge transfer bands of the benzoate chromophores. This relationship (figure 18) was such that positive chirality gave rise to a positive first cotton effect and a negative chirality gave rise to a negative first cotton effect.



positive chirality

positive first C.E.



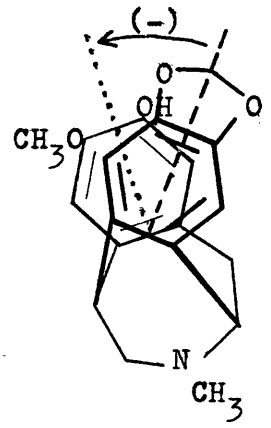
negative chirality

negative first C.E.

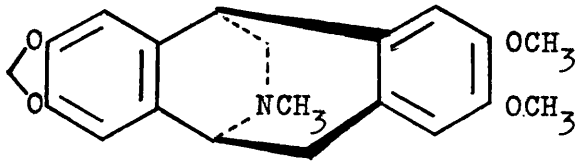
(18)

In a subsequent publication[21] Nakinishi showed that this aromatic chirality rule could be extended to other aromatic chromophores for which the directions of the two interacting transitions were known.

Shamma and Moniot applied this rule to the isopavinane alkaloid (-) amurensine (19) and thus deduced the configuration shown (20)[22]. Furthermore, they extended this absolute configuration to all pavinanes and isopavinanes which, like amurensine, exhibit a negative specific rotation at the sodium D line.



(19)



(20)

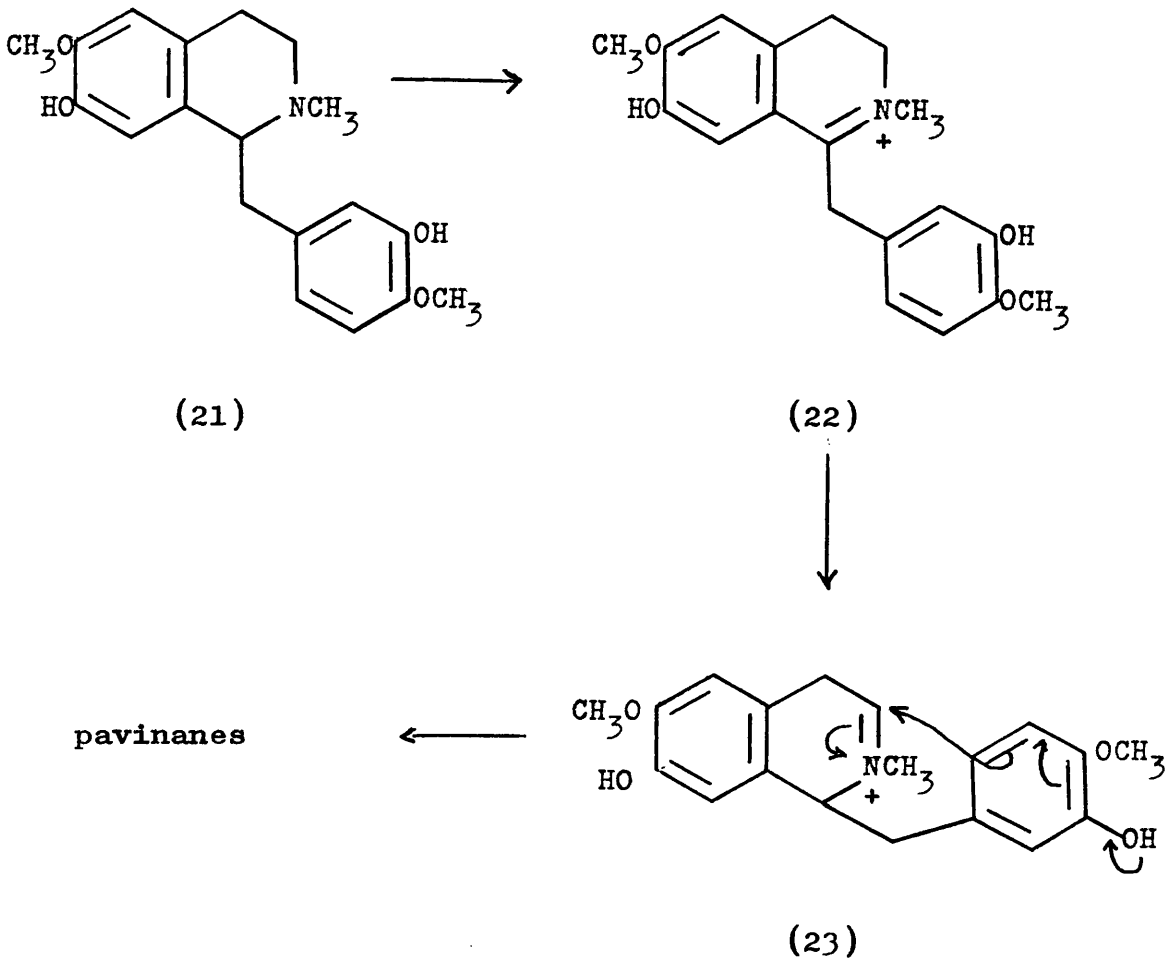
negative chirality

negative first C.E.

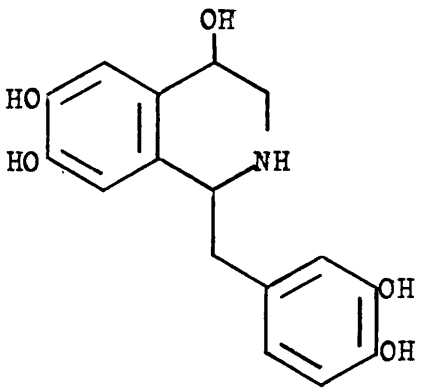
Biosynthesis

It had always been supposed[14,23] that the pavinane alkaloids were biosynthesised from reticuline (21). However, feeding experiments were inconclusive. When ^{14}C-labelled reticuline was fed to Argemone mexicana L., the argemonine isolated was not radioactive[23], but this may have been due to the fact that only very small amounts of argemonine are present in this plant[24]. In view of the known[25] dehydrogenation of reticuline to (22), Stermitz and Seiber postulated[24], that the 3,4-dihydroisoquinoline (22) could isomerise to (23) followed by cyclisation to the pavinane system.

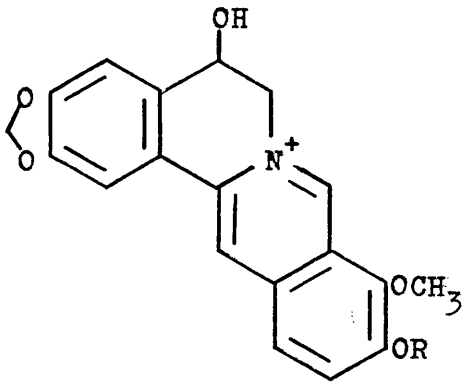
The fact that the pavinane and isopavinane alkaloids have similar absolute configurations, provides support for the postulate advanced by Dyke[26] that both might be derived from a common biogenetic precursor. Dyke and his co-workers had speculated[26-28] that 4-hydroxynorlaudanosoline (24) might be the formal precursor of a diverse group of alkaloids



resembling those derivable from norlaudanosine itself[29]. Support for this postulate was provided by the isolation from natural sources of alkaloids bearing an oxygen substituent at C-4 of the isoquinoline moiety such as berberastine (25a)[30,31], thalidastine (25b)[32], tetrahydroberberastine[30], stephorphine (26a)[33], cataline (26b)[34], imenine (27)[35], erythrinine (28a)[36] and erythistemine (28b)[37]. The 4-hydroxynorlaudanosoline could arise from noradrenaline (29) which has been detected in a number of plant species[38]. It has been shown that noradrenaline is the precursor of berberastine in Hydrastis canadensis.[30,31]

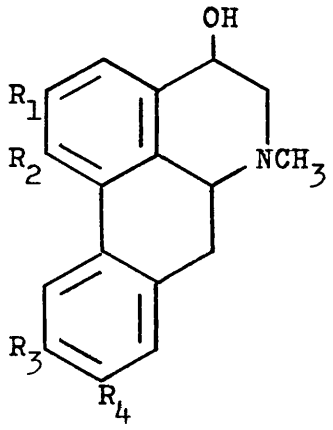


(24)

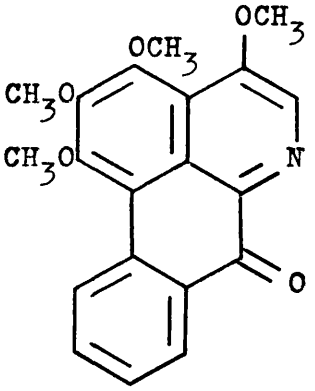


(25a) R = CH_3

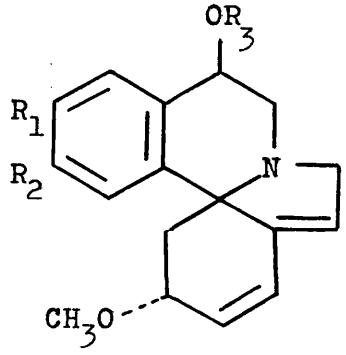
(25b) R = H



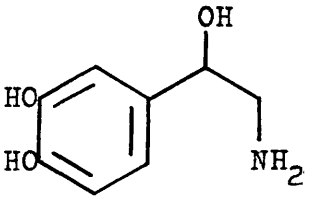
	R_1	R_2	R_3	R_4
(26a)	O-CH_2-O		H	H
(26b)	OCH_3	OCH_3	OCH_3	OCH_3



(27)

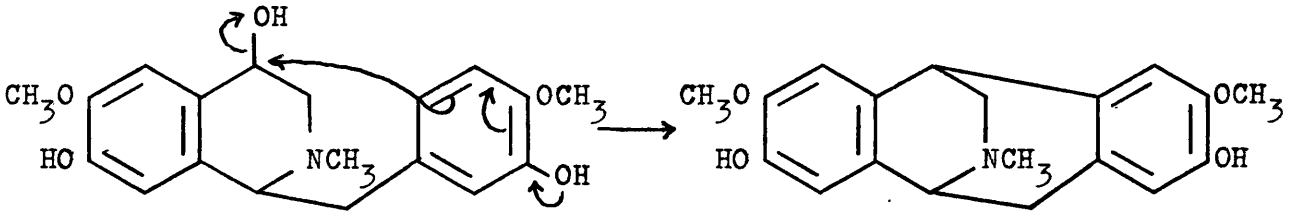


	R_1	R_2	R_3
(28a)	O-CH_2-O		H
(28b)	OCH_3	OCH_3	CH_3



(29)

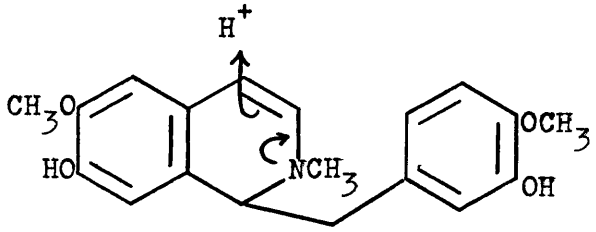
Dyke therefore postulated[26] that 4-hydroxynorlaudanosoline might be the common biogenetic precursor of both the pavinane and the isopavinane alkaloids. Partial methylation would afford 4-hydroxy reticuline (30) which, depending on the plant family or genus, could cyclise directly to an isopavine species, or alternatively undergo dehydration, protonation and cyclisation to a pavine analogue (scheme 4).

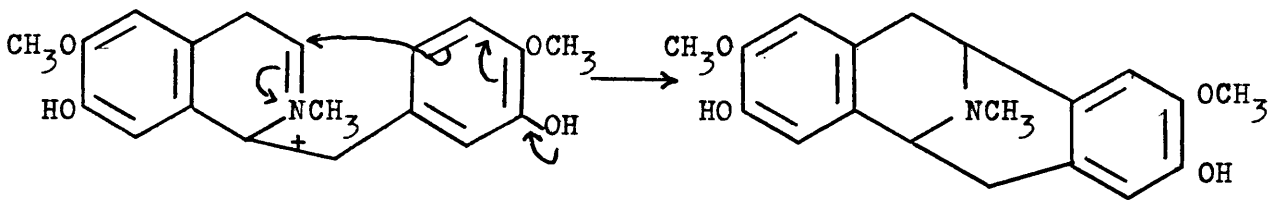


(30)

ISOPAVINANE

$-H_2O$

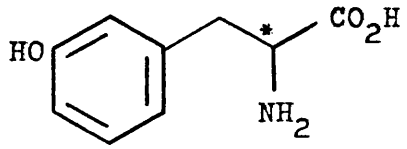




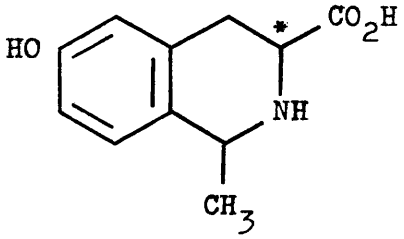
PAVINANE

Scheme 4

It is generally accepted that in the biosynthesis of the isoquinoline ring, DOPA is first decarboxylated to dopamine, and, it is known that when ^{14}C-labelled dopamine is fed to plants that produce alkaloids of the isoquinoline group, the products are specifically labelled. However, it has been shown that when (±)-m-tyrosine-2-^{14}C (31) is fed to Euphorbia myrinites, the alkaloid (32) can be isolated, specifically labelled[39].



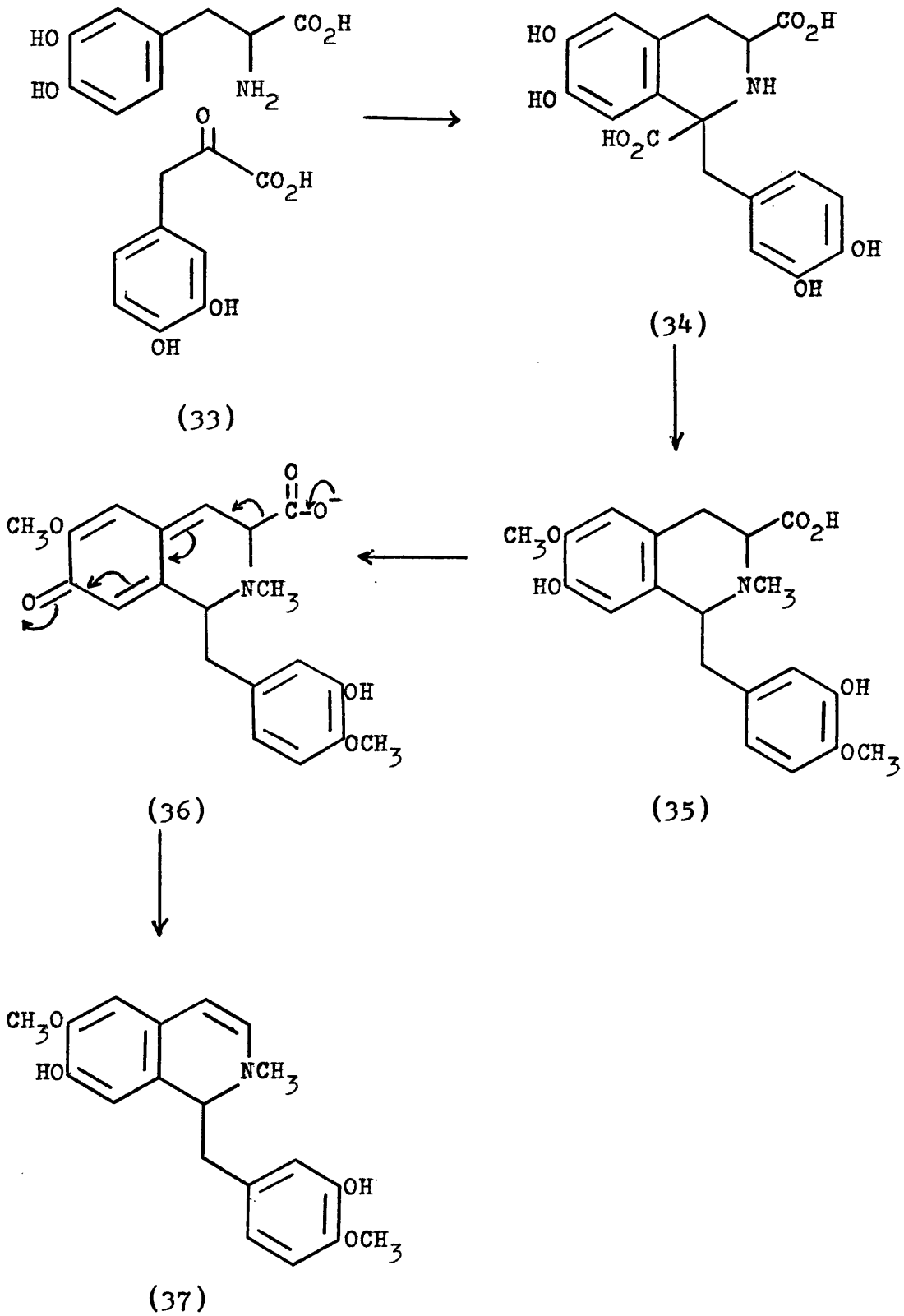
(31)



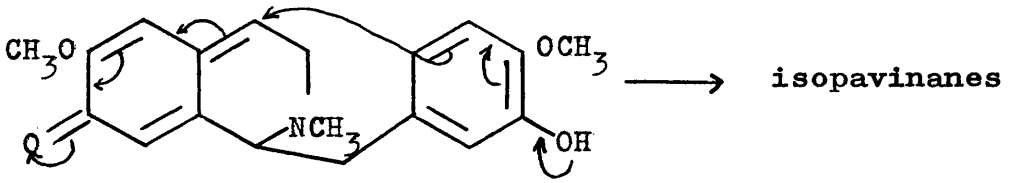
(32)

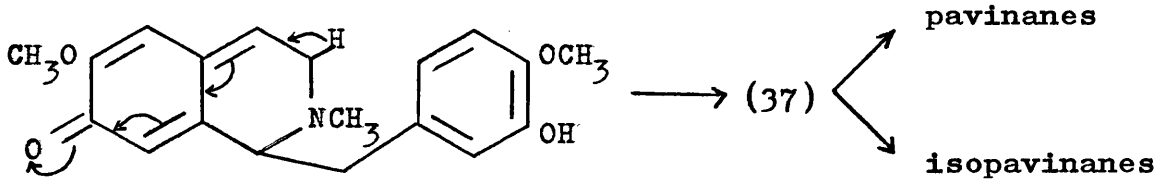
It is therefore reasonable to postulate that direct condensation of DOPA with an α keto acid such as (33) could occur to give the isoquinoline-1,3-dicarboxylic acid (34). This could then undergo loss of the C_1 carboxyl group and methylation to give a 1-benzyltetrahydroisoquinoline-3-carboxylic acid such as (35). An alternative mode of biosynthesis of pavinanes could then involve oxidative decarboxylation via the quinone methide (36) to give the 1,2-dihydroisoquinoline (37) which could undergo protonation and cyclisation to the pavinane (see scheme 4). To explain the formation of isopavinanes on this basis, it would be necessary to postulate hydration of the 1,2-dihydroisoquinoline (37) to give the corresponding 4-hydroxytetrahydroisoquinoline

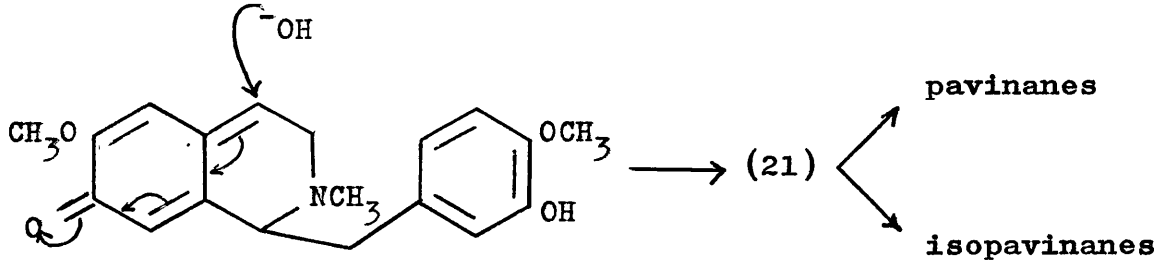
which could then cyclise to the isopavinane as shown in scheme 4. Such hydrations are known in vitro[28].



Alternatively both pavinanes and isopavinanes could arise from reticuline by initial oxidation to the quinone methide (38), followed by cyclisation, rearrangement to (37) or hydration to 4-hydroxyreticuline (30) followed by further reactions as discussed above. Examples of C_4 - hydroxylation of 7-hydroxytetrahydroisoquinolines <u>in vitro</u> involving oxidation with lead tetraacetate have been reported[40].



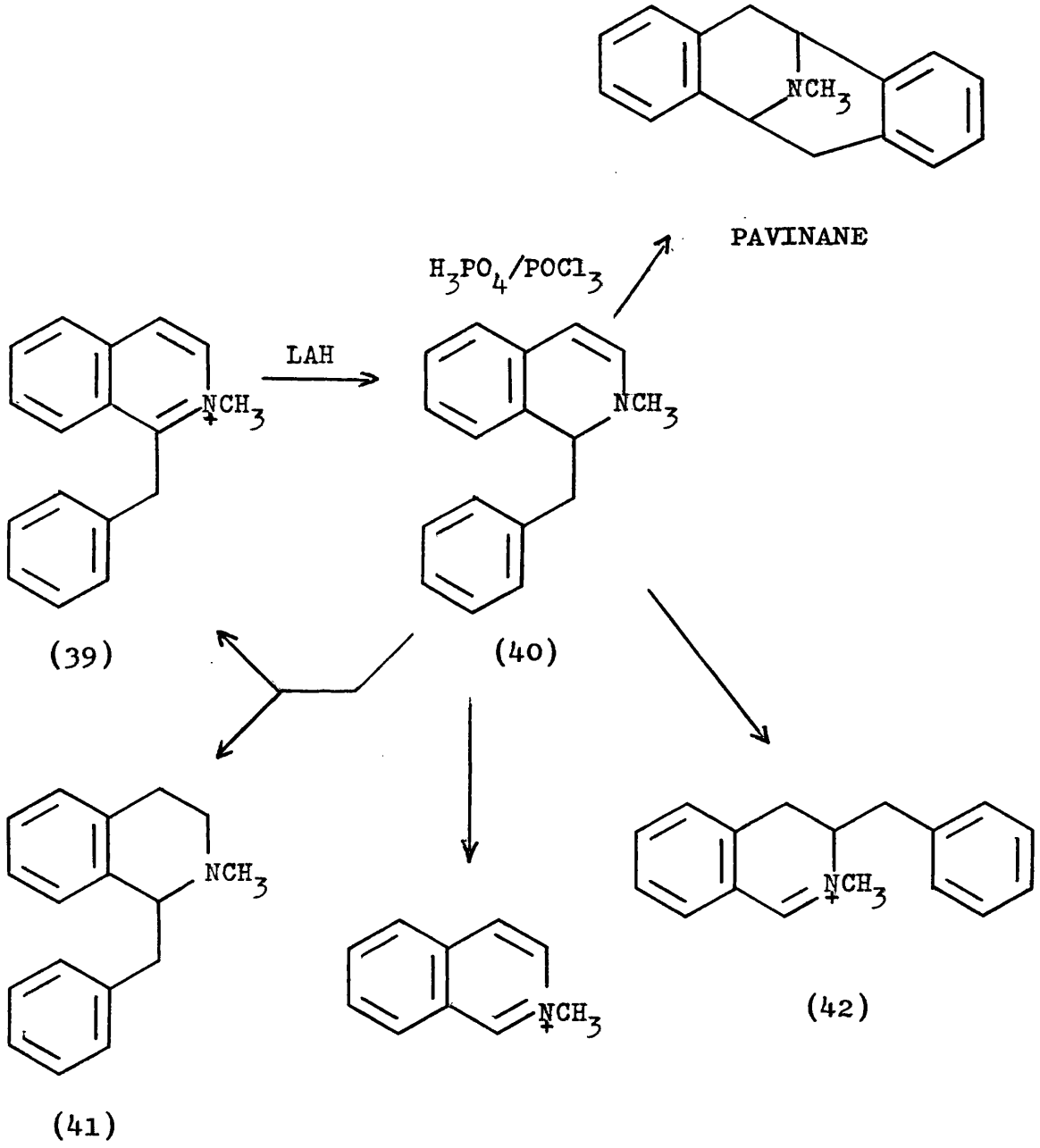




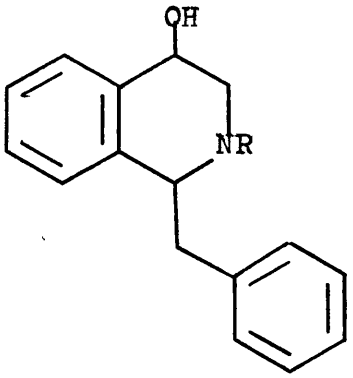
So at this time the biosynthetic route to the pavinane and isopavinane alkaloids is unknown.

Synthesis

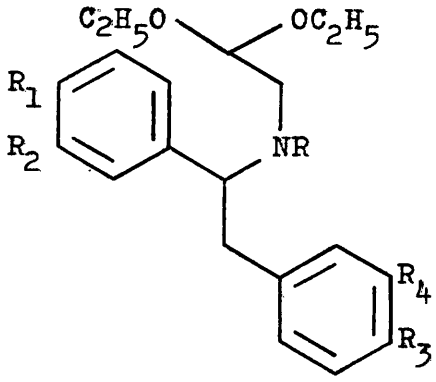
Until recently the only synthesis of the pavinane ring system involved partial reduction of 1-benzyl-2-methyl-isoquinolinium salts such as (39) to the corresponding 1,2-dihydroisoquinoline (40), followed by acid catalysed cyclisation, usually with phosphoric acid/phosphor us oxychloride mixtures at elevated temperatures (120-150°). Yields were frequently poor due to side reactions of the unstable 1,2-dihydroisoquinoline which included, dimerization, disproportionation to the quaternary salt (39) and the 1,2,3,4-tetrahydroisoquinoline (41)[41], elimination of the 1-benzyl group[42] and rearrangement to the 3-benzyl-3,4-dihydroisoquinolinium salt (42).[41,43,44,45] Early attempts[14] to establish the conditions for preferential pavinane formation or rearrangement were inconclusive; however a more extensive investigation using 2-methyl-1,2-dihydropapaverine has been described[45]. It has recently been demonstrated[46] that improved yields of pavinane can be obtained using high dilutions since the side reactions such as disproportionation and rearrangement are bimolecular processes. A further disadvantage of this method is that it cannot be used for the synthesis of compounds containing methylenedioxyfunctions, as these are cleaved by the severe conditions required for cyclisation[14]. Also, 1-benzyl-isoquinolines with the required oxygenation pattern are not always accessible[43,47] and finally, because it has not proved possible to resolve the intermediate acid labile 1,2-dihydro-isoquinolines[14], only racemic pavinanes are accessible by this route.



Isopavinanes have been prepared by acid catalysed cyclisation of 1-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolines (43). The required 4-hydroxy compounds, which are not usually isolated, have been prepared by hydroboration and oxidation of 1-benzyl-1,2-dihydroisoquinolines[28,48] by lead tetraacetate oxidation of 1-benzyl-7-hydroxy-1,2,3,4-tetrahydroisoquinolines[40,49] or most usefully, by acid catalysed cyclisation of benzylaminoacetaldehyde dialkylacetals of the type (44)[28,50]



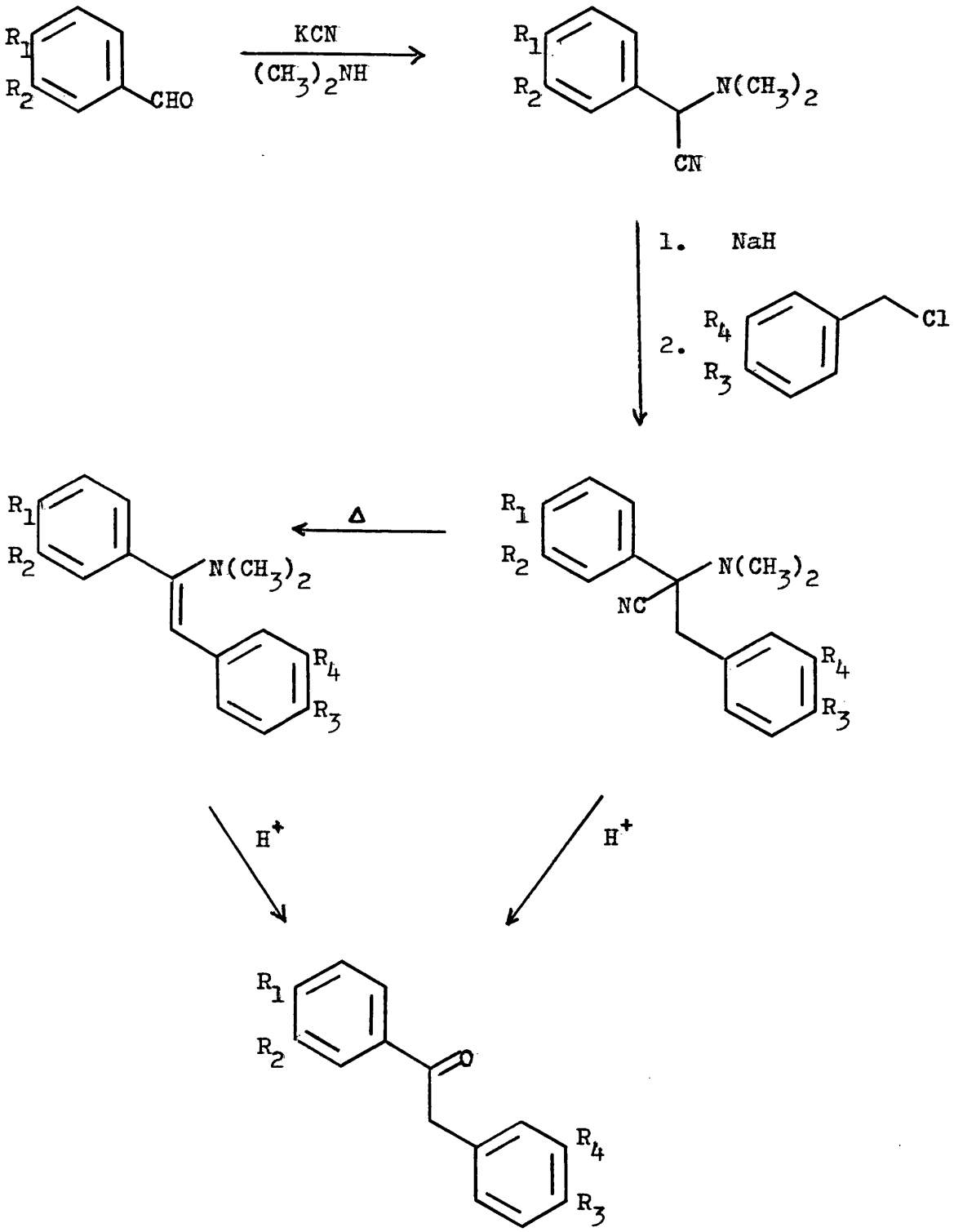
(43)



	R_1	R_2	R_3	R_4	R_5
(44a)	OCH_2Ph	OCH_3	$O\text{-}CH_2\text{-}O$		CH_3
(44b)	OCH_3	OCH_2Ph	$O\text{-}CH_2\text{-}O$		CH_3
(44c)	OCH_2Ph	OCH_3	$O\text{-}CH_2\text{-}O$		CH_3

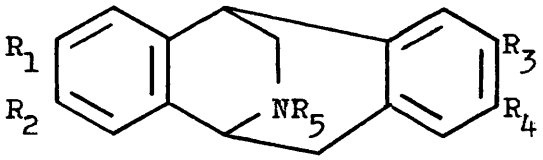
Several routes to the required benzylaminoacetals (44) are available, condensation of aminoacetaldehyde dialkylacetal with the appropriately substituted deoxybenzoin followed by reduction of the resultant Schiff's base being the most common.[8,26,27,28]

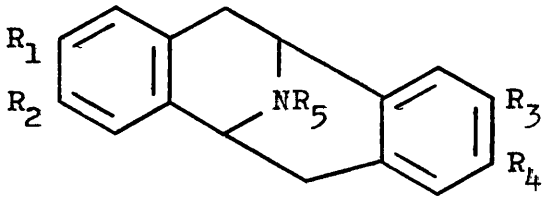
Although a number of methods for preparing deoxybenzoins are known[51-56] none of them was suitable for the preparation of unsymmetrically substituted derivatives in which the aromatic rings carried OH, OCH_3 or methylenedioxy functions. This prompted the development of a new method for synthesising deoxybenzoins, outlined in scheme 5.[57,58]



Scheme 5

It was recently reported[50] that when the acetals (44a) and (44b) were treated separately with 6N HCl the expected isopavinanes (45a) and (45b) were accompanied by the corresponding pavinanes (46a) and (46b). This was the first time that pavinane cyclisation had been observed under such mild conditions. It has since been found[59] that cyclisation of the benzylaminoacetal (44c) affords the pavinane (46c) in 40% yield, with only trace amounts of the isopavinane being detected on this occasion. It is not known at what stage the benzyloxygroups are cleaved.

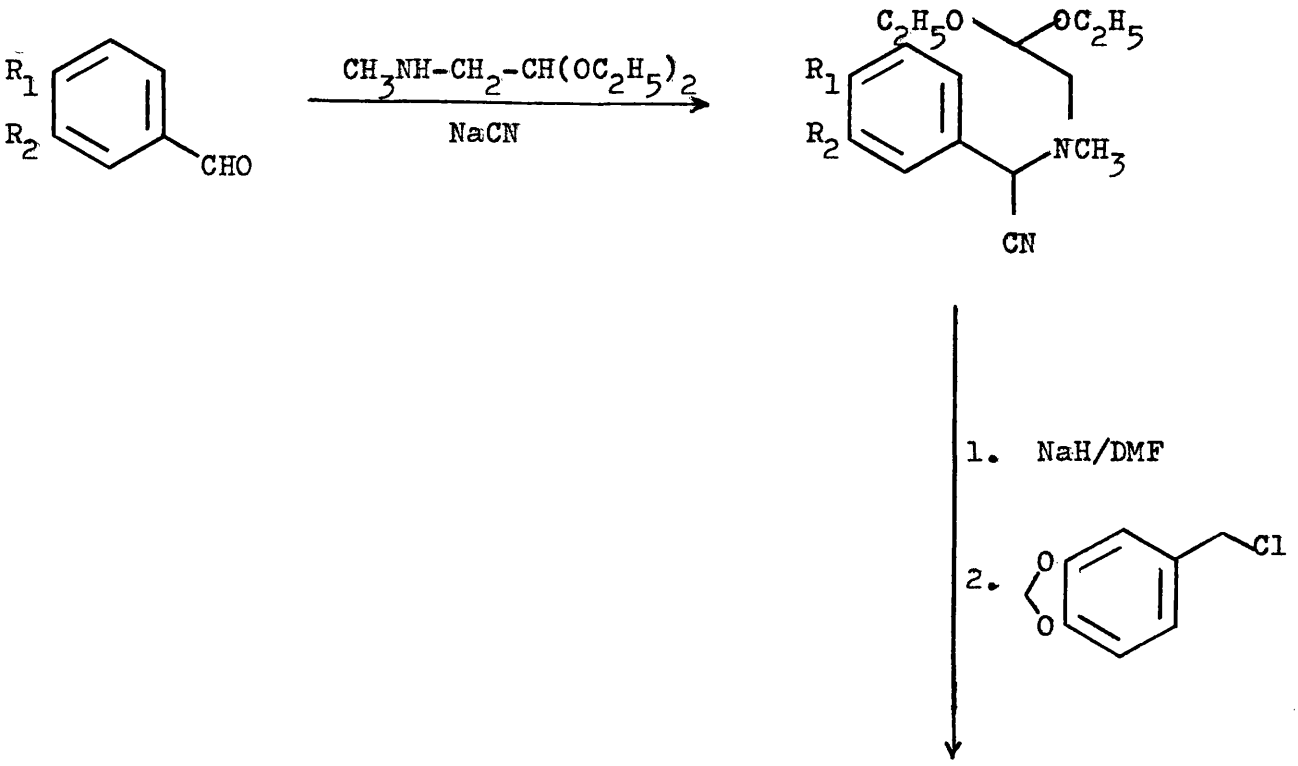




	R_1	R_2	R_3	R_4	R_5
(45a)	OH	OCH_3	O-CH_2-O		CH_3
(45b)	OCH_3	OH	O-CH_2-O		CH_3

	R_1	R_2	R_3	R_4	R_5
(46a)	OH	OCH_3	O-CH_2-O		CH_3
(46b)	OCH_3	OH	O-CH_2-O		CH_3
(46c)	OH	OCH_3	O-CH_2-O		H

The acetals (44a) and (44b) were prepared by the route shown in scheme 6.

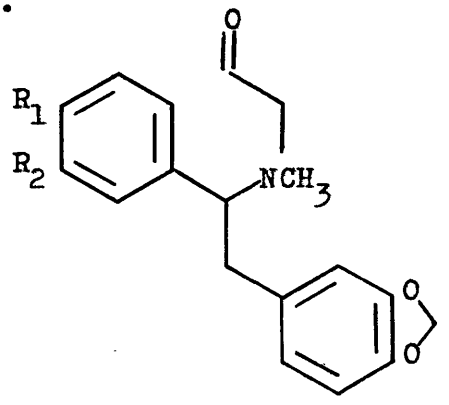


(44a) $R_1 = OCH_2Ph$, $R_2 = CH_3O$

(44b) $R_1 = OCH_3$, $R_2 = OCH_2Ph$

Scheme 6

It was also reported[50] that acid treatment of the aldehyde (47b) resulted in the formation of both (45b) and (46b); however cyclisation of (47a) afforded only the isopavinane (45a).

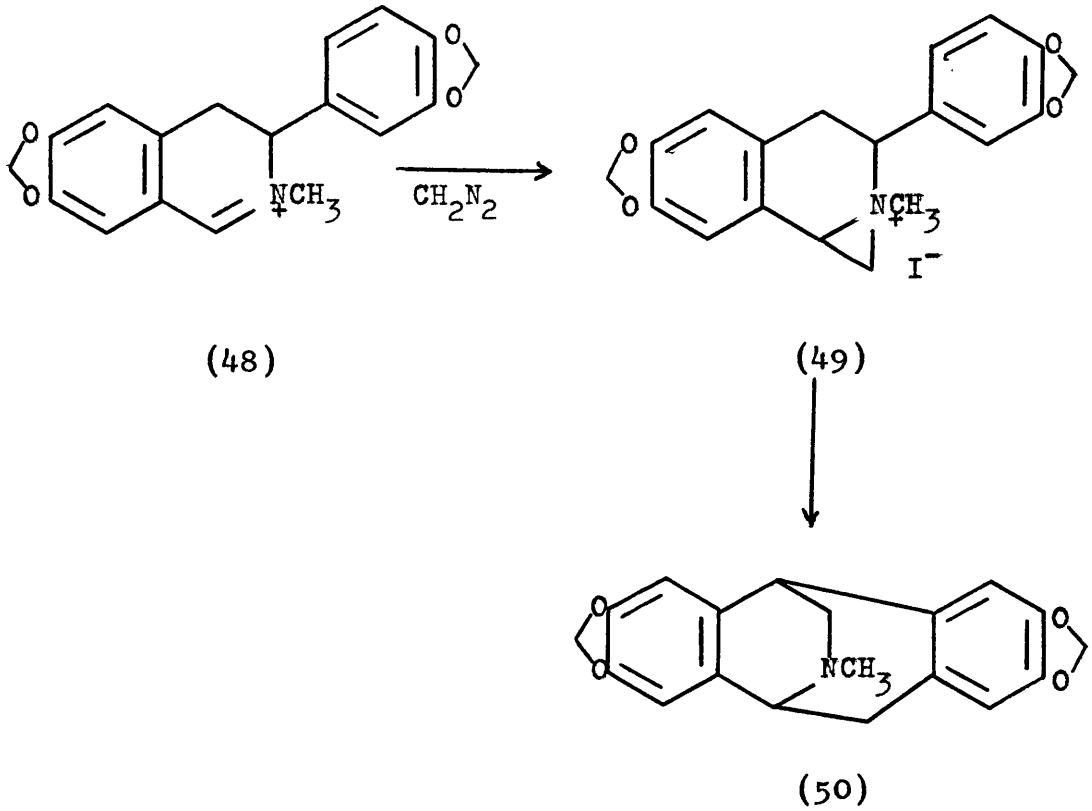


(47a) $R_1 = OCH_2Ph$, $R_2 = OCH_3$

(47b) $R_1 = OCH_3$, $R_2 = OCH_2Ph$

The mixtures of products in the above reactions were explained in terms of a 4-hydroxy-1,2,3,4-tetrahydroisoquinoline intermediate, which could either undergo direct cyclisation to the isopavinane, or alternatively, undergo dehydration, protonation and cyclisation to the pavinane (c.f. scheme 4). The ratio of isopavinane to pavinane formation could be expected to depend upon such factors as the nitrogen substituent, the pH and the nature and position of oxygen functions attached to the aromatic rings. For example, a 1-(3,4-methylenedioxybenzyl) group might be expected to be a weaker nucleophile than a 1-benzyl group with a methoxy or hydroxy group para to the point of ring closure. Thus, in the case of a 1-(3,4-methylenedioxybenzyl) function nucleophilic displacement of the 4-hydroxy group in the intermediate 4-hydroxytetrahydroisoquinoline, to give the isopavinane may be slow, allowing more time for dehydration to the 1,2-dihydroisoquinoline and hence pavinane formation to occur.

Using a previously devised ring expansion reaction[60], Kametani synthesised (±) reframidine (50) as well as other isopavinanes[61,62] (scheme 7). Treatment of the hydrastinine derivative (48) with diazomethane gave the aziridium salt (49) which, when subjected to strong acid, afforded (±) reframidine (50) in 20% yield.



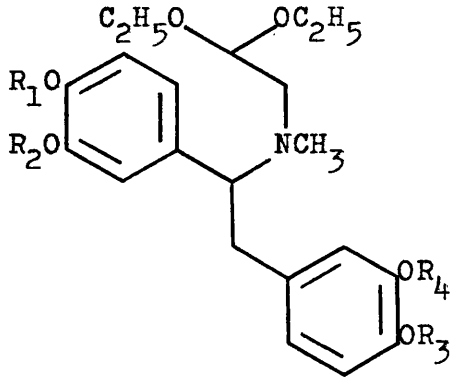
(48) (49) (50)

Scheme 7

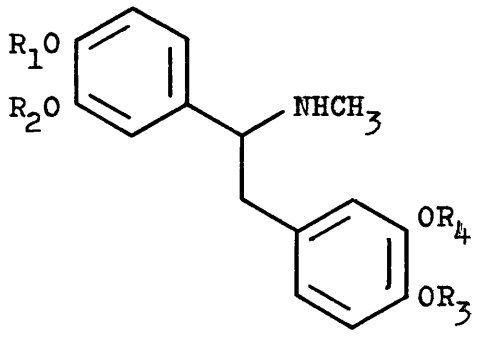
From the above discussion it can be seen that when this work began the absolute configuration of the isopavinane alkaloids rested upon the interpretation of the C.D. data acquired for reframoline. Whilst the interpretations made by Shamma and Moniot were not seriously in question, it was highly desirable that some independent evidence should be sought to confirm the predictions made. The discussion and experimental sections of this chapter describe a successful attempt to prove the absolute stereochemistry of the isopavinane alkaloids by synthesis of an optically active member of this group from an intermediate of known absolute stereochemistry.

DISCUSSION

It was decided to attempt to prove the absolute configuration of the isopavinane alkaloids by synthesis of an optically active member of this group from an optically active benzylaminoacetal of the type (51), of known configuration. Previous attempts to resolve acetals of the type (51) with the (+) and (-) forms of dibenzoyltartaric acid proved unsuccessful due to hydrolysis of the acetal function. However, 1,2-diarylethylamines of the type (52) have been successfully resolved in this laboratory[44] and furthermore, conversion to the corresponding acetals (51) has been achieved by refluxing with bromoacetal in D.M.F. It has also been shown[44] that racemisation of the optically active 1,2-diarylethylamines does not occur under the conditions employed in the alkylation with bromoacetal.



(51)

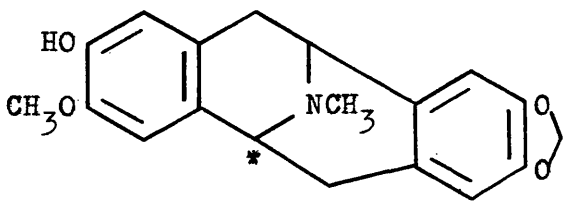


(52)

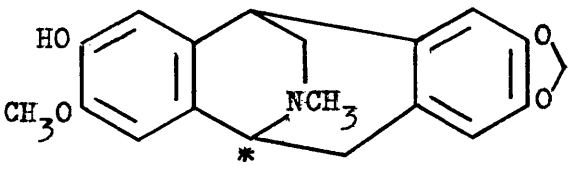
Nakazaki had shown[63], that (-)-1,2-diphenylethylamine has the R configuration, by degradation of its (+)-N-acetyl derivative to D-aspartic acid, and this assignment was supported by an independent o.r.d. study[64]. Hence, it might

have been possible to determine the absolute configuration of the 1,2-diarylethylamine (52) by comparison of its o.r.d. spectrum with that of (-)-R-1,2-diphenylethylamine. However, in view of the fact that a chromophore is directly attached to the chiral centre, it was thought that the validity of extrapolating such data to derivatives of the type (52) with oxygen substituents attached to the aromatic rings might be questionable.

In view of the reported formation of both pavinane and isopavinane skeleta by acid-catalysed cyclisation of the appropriately substituted benzylaminoacetal (51) (see page 24), the author decided to exploit this dual synthesis in the determination of the absolute stereochemistry of the isopavinane alkaloids. It was anticipated that acid-catalysed cyclisation of an optically active sample of (51, R_1=$PhCH_2$, R_2=CH_3, R_3R_4= $-CH_2-$), would afford an optically active sample of the pavinane caryachine (53) and an optically active sample of the isopavinane reframoline (54). As the absolute stereochemistry of the pavinane (-)-caryachine had been firmly established (see page 11), the sign of the optical rotation of the synthetic caryachine would automatically establish the absolute configuration of the acetal and hence of the synthetic reframoline.

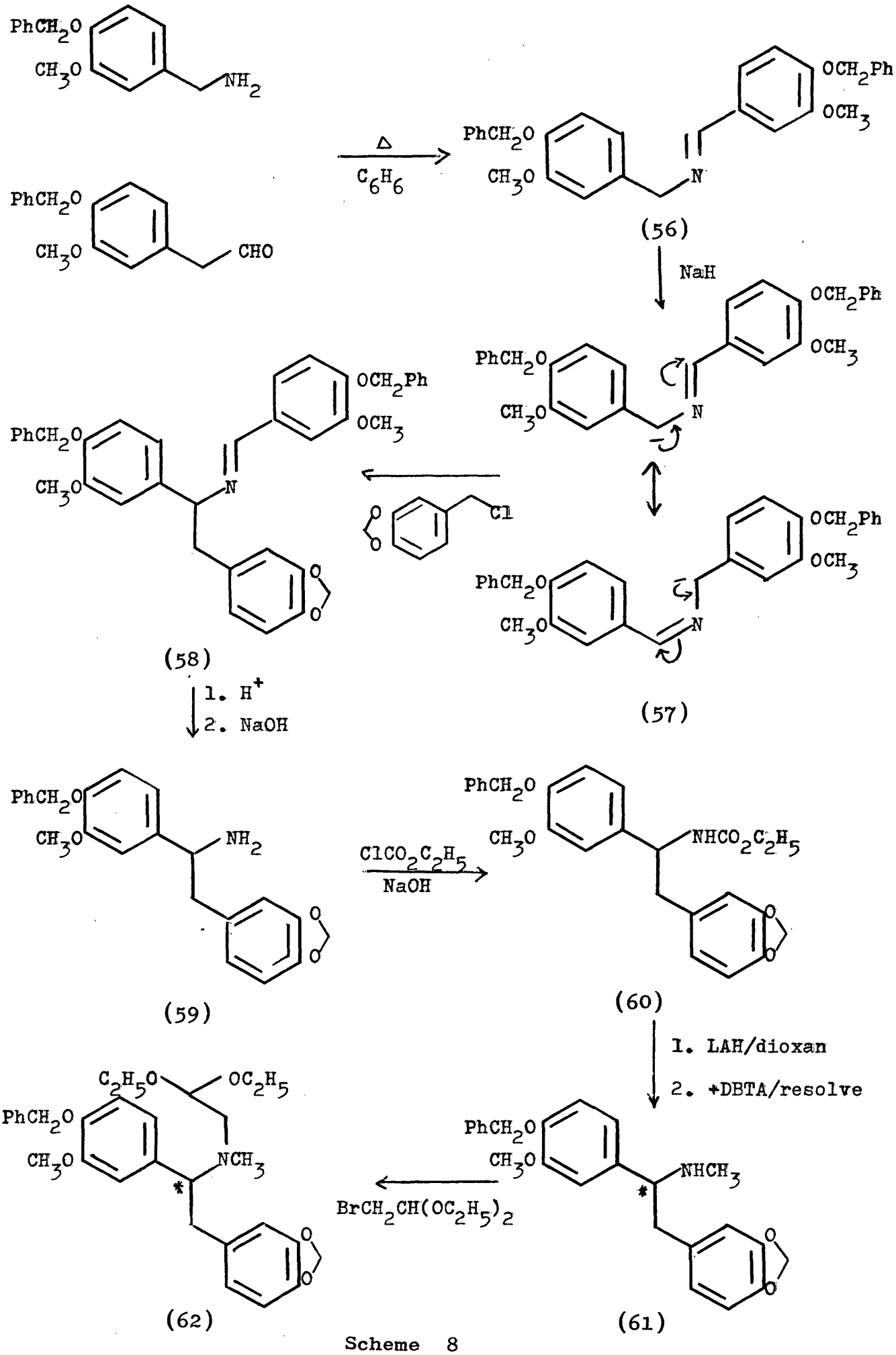


(53)



(54)

Various attempts had been made in this laboratory to prepare benzylbenzylamines of the type (52)[65]. The method chosen by the author which is outlined in scheme 8 had been previously successfully employed[50] and was based on experiments described in a private communication from Professor A R Battersby. O-Benzylvanillylamine (55) was prepared by reduction of the oxime of O-benzylvanillin with zinc and acetic acid. Difficulty was encountered in the work-up of this reaction due to the insolubility in water of the acid salts of the amine. The amine was heated under partial reflux with an equimolar quantity of O-benzylvanillin in benzene to afford the Schiff's base (56) as a yellow gum. Although the product could be crystallised from absolute ethanol, the crystal structure was lost upon drying, even at room temperature in vacuum. The Schiff's base was stirred with sodium hydride in dry DMF under an atmosphere of dry nitrogen, whereupon a wine red colouration developed due to formation of the symmetrical anion (57). A solution of piperonyl chloride in dry DMF was then added with the result that the red colour was rapidly discharged. The resultant straw coloured solution was stirred overnight at room temperature and then excess sodium hydride was destroyed by addition of methanol. The solvent was removed at 60° under reduced pressure and the yellow residue stirred with benzene and 2M HCl, whereupon the hydrochloride of (58) precipitated in 40% yield. After this initial success, numerous attempts to repeat this reaction resulted in failure, a sticky yellow gum consisting of an inseparable



Scheme 8

mixture of products being obtained on each occasion. The purity of the reagents used in both the formation of the Schiff's base and the alkylation reaction were carefully examined and found to be satisfactory. Variations in temperature, concentrations, the time allowed for anion formation or the rate of addition of the piperonyl chloride failed to lead to the success of the reaction.

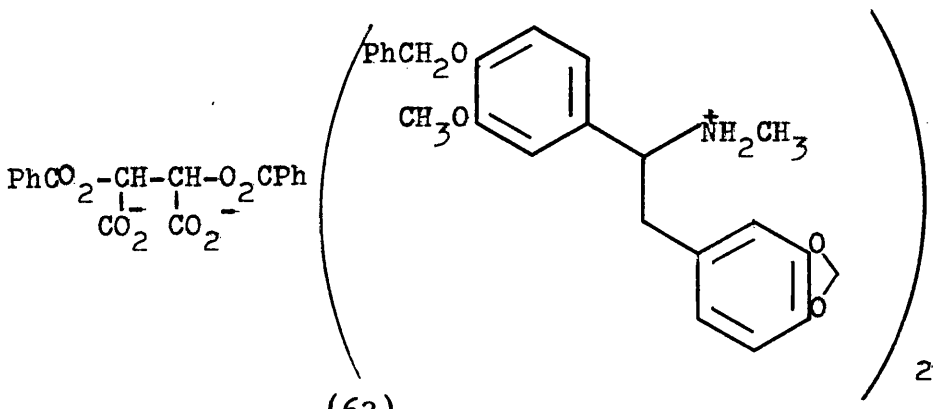
At this stage the author started to examine an alternative route to the required amine (59)

However, shortly after commencing work on this alternative synthesis, the solution to the problem in the above alkylation reaction was found. In the work-up of one of the alkylation reactions a transient red colour was observed during removal of the solvent. It was concluded that as the concentration of the mixture increased at 60^{o} the sodium methoxide resulting from decomposition of the excess sodium hydride was abstracting protons to form anions which were reacting further to give the inseparable mixture of products obtained. This problem was overcome by acidifying the mixture with acetic acid just prior to the removal of the solvent. In all subsequent alkylation experiments yields of (59) were in excess of 70%.

Attempts to form the N-methylamine (61), by quaternisation of the alkylated Schiff's base (58) with methyliodide in benzene, prior to hydrolysis failed, giving black tarry mixtures of products. The required N-methylamine was eventually prepared by reduction of the N-carbethoxy ester (60). Previously reported[50,65] conditions for the formation of the

carbamate (60) were found to be unsatisfactory. However, good yields of (60) were obtained under phase transfer conditions by adding ethylchloroformate dropwise to the primary amine (59) dissolved in diethyl ether and stirred with 2M sodium hydroxide. The product precipitated upon evaporation of the ether and could be crystallised from methanol. Reduction of this carbamate with lithium aluminium hydride in boiling dioxan afforded the N-methylamine (61).

Attempts to resolve the amine (61) using a 1:1 molar ratio of (+)-dibenzoyltartaric acid (+ DBTA) in a number of different solvents were unsuccessful. However, repeated recrystallisations of the disalt (63) formed from a 2:1 molar ratio of (61) and (+) - DBTA in ethanol afforded the (+)-enantiomer of (61) as a colourless oil with an $[\alpha]_D^{20}$ of $+87.3^{\circ}$. That the salt formed with (+) DBTA was the disalt (63), was confirmed by quantitative regeneration of the amine (61) from a known weight of the salt and by nmr spectroscopy, by comparing the integral over the ortho protons of the O-benzoyl functions with the integral over the methylenedioxy protons.



(63)

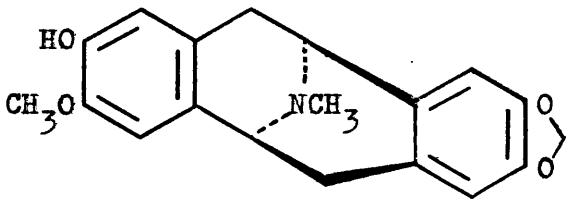
Subsequent steps of the synthetic route were developed using racemic compounds before being applied to the synthesis of the optically active compounds.

The amine (61) in dry DMF was treated dropwise with excess bromoacetal at 100° over an 8 hour period. The mixture was stirred at 100° and the progress of the reaction followed by periodic sampling and G.C. comparison with a sample of pure (61). After 24 hours the crude product was shown by nmr to consist of an approximately 60:40 mixture of the required acetal (62) and the starting amine (61). Reaction was complete after 36 hours as indicated by the fact that no further change occurred in the G.C. trace. The nmr spectrum of the crude product showed it to be contaminated with approximately 20% of unchanged starting material which was removed by column chromatography on alumina using benzene - chloroform elution. The pure acetal (62) was a colourless oil with an $[\alpha]_D^{20}$ of +67.2°

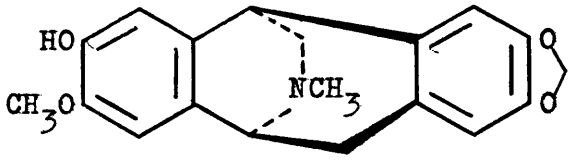
The acetal (62) was treated with 1:1 ethanol - cHCl at room temperature overnight and then under reflux for 6 hours. Thin layer chromatography of the crude bases from this reaction showed two major components and comparison with the previously prepared sample[50] indicated these to be the required isopavinane and pavinane. Column chromatography on silica using chloroform - methanol elution afforded (-)-reframoline as a beige amorphous solid with $[\alpha]_D^{20}$ of -144° in ethanol (lit[6] -140° in methanol) and (1)-caryachine, also as a beige amorphous solid with $[\alpha]_D^{20}$ of -251° in ethanol (lit[64] -270° in methanol). The UV and nmr spectra

of the products were very similar, with the latter showing four aromatic protons resonating as singlets in each case. The products were distinguished by their mass spectral fragmentation patterns (see page 7). In addition to a strong molecular ion and $(M-1)^+$ peak, the mass spectrum of the synthetic reframoline showed a fairly strong peak at m/e $282(M-43)^+$ due to the ion formed by retro Diels-Alder loss of the nitrogen bridge. This peak was absent in the spectrum of caryachine, the characteristic feature of which was the appearance of two peaks of almost equal intensity due to the two isoquinolyl fragments.

Since the absolute configuration of (-) caryachine had been firmly established as 5S, 11S (64) by Battersby[14], it followed that both the acetal (62) and the preceding 1,2-diarylethylamine (61) must have the S-configuration. Hence the isopavinane alkaloid (-) reframoline must have the 5S, 10S configuration (65).



(64)



(65)

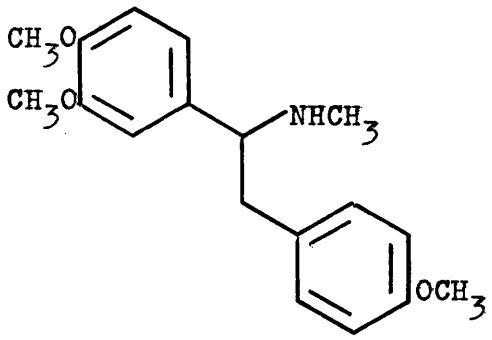
C.d. Spectra

A characteristic feature of the c.d. curves of many dissymmetric molecules containing two similar non conjugated chromophores, is the appearance of bisignate circular dichroism (a couplet) associated with each of the isotropic absorption bands. Each band gives two strong cotton effects of the same amplitude but opposite sign separated from each other by Davydov splitting ($\Delta\lambda$). This phenomenon termed exciton splitting or Davydov splitting, is due to coupling between the excitation moments of the two chromophores and is observed only if the chromophores are held fairly rigidly in a dissymmetric arrangement. The c.d. of coupled chromophores often lacks the expected exciton form and even when bisignate curves are obtained, the rotational strengths of the two oppositely signed components are not equal in magnitude contrary to the predictions of simple theory.

The c.d. spectrum of the synthetic pavinane (-)-caryachine was very similar to that of natural (-)-argemonine[15] showing the expected exciton splitting. The spectrum exhibited a bisignate cotton effect centred at 293nm with maxima at 298nm ($\Delta\varepsilon$ = -1.69) and 280nm ($\Delta\varepsilon$ = +3.86). However unlike the c.d. spectrum of (-)-amurensine, the c.d. spectrum of the synthetic isopavinane (-)reframoline did not exhibit the expected exciton splitting showing a maximum at 296nm ($\Delta\varepsilon$ = -1.61).

The c.d. spectrum of the (+)-1,2-diarylethylamine (61) was very similar to that of the dextrorotatory isomer of the trisubstituted derivative (66), thus establishing the

S-configuration for the latter.



(66)

This work represents the first reported synthesis of both the pavinane and isopavinane systems in an optically active form and offers confirmation of the stereochemistry of the isopavinane alkaloids, deduced by Shamma by application of the aromatic chirality rule.

EXPERIMENTAL

3,4-methylenedioxybenzyl alcohol

Sodium borohydride (8g) was added portionwise to a stirred solution of 3,4-methylenedioxybenzaldehyde (60g) in 95% EtOH ($200cm^3$) at room temperature. After stirring for 90 minutes, the solvent was removed and the residue dissolved in $CHCl_3$ ($250cm^3$). The resultant solution was washed with H_2O ($1x100cm^3$), dried (Na_2SO_4) and evaporated to yield the required alcohol as an oil, which crystallised on standing. The product crystallised from petrol (60-80°) as colourless needles (95%) mp 49-50.5° ν max (5%w/v CCl_4) $3360cm^{-1}$ (OH). nmr ($CDCl_3$) 6.9-6.5 complex [3] (Ar-H), 5.87s [2] (O-CH_2-O), 4.5 partially resolved doublet [2] collapsed to singlet on deuteration (-$C\underline{H}_2$-OH), 2.22 broad s [1] (OH) removed by D_2O.

3,4-methylenedioxybenzylchloride

Thionyl chloride (18g) was added dropwise to an ice cold, stirred solution of 3,4-methylenedioxybenzyl alcohol (20g) in dry ether ($60cm^3$). After stirring for 1 hour, the solvent and excess $SOCl_2$ were removed under reduced pressure. The residual oil was dissolved in Et_2O ($100cm^3$), washed with 2M Na_2CO_3 ($2x50cm^3$), H_2O ($50cm^3$), dried (Na_2SO_4) and evaporated to give the chloride as a colourless oil (92%), ν max $690cm^{-1}$.

3-methoxy-4-benzyloxybenzaldehyde

Vanillin (152g) in 95% EtOH ($300cm^3$) and NaOH (60g) in H_2O ($150cm^3$) were heated under reflux for 30 minutes. Benzyl chloride (126.5g) was then added dropwise with stirring.

The mixture was refluxed for a further 6 hours and then chilled to 5° overnight, whereupon the required product crystallised. The product was filtered off, washed with Et_2O and recrystallised from EtOH. Yellow needles (60%) mp 63-64°. ν max (5%w/v in CCl_4) 1700cm^{-1}, nmr ($CDCl_3$) 9.8s [1] (CHO), 7.6-7.2 complex [7] (7xAr-H), 6.98d J=8Hz [1] (Ar-H_5), 5.22s [2] (Ph-$C\underline{H}_2$-O), 3.92s [3] (OCH_3).

3-methoxy-4-benzyloxybenzaldoxime

Hydroxyammonium chloride (10.5g) in H_2O (12.5cm^3) was added to a stirred solution of 3-methoxy-4-benzyloxybenzaldehyde (30.2g) in warm 95% EtOH (50cm^3). A solution of NaOH (7.5g) in H_2O (10cm^3) was then added portionwise and the mixture left to stand overnight. Crushed ice (80g) was added and the resultant slurry saturated with CO_2. The product was filtered off, washed with H_2O (3x30cm^3) and dried. White needles (93%). mp 109-111° ex EtOH, ν max 3260 (N-OH) nmr ($CDCl_3$). 10.38 broad s [1] removed by D_2O (=N-OH), 8.05s [1] (-CH=N-), 7.6-7.1 complex [6] (6xAr-H) 7.0 d.d J ortho = 8Hz, J meta = 1-2Hz (Ar-H_6), 6.86 d J=8Hz (Ar-H_5), 5.14s [2] (Ph-$C\underline{H}_2$-O), 3.88s [3] (OCH_3) (Found C 69.9, H 5.9, N 5.6, $C_{15}H_{15}NO_3$ requires C 70.0, H 5.8, N 5.5%).

3-methoxy-4-benzyloxybenzylamine (55)

Zinc dust (30g) was added portionwise to a stirred solution of 3-methoxy-4-benzyloxybenzaldoxime (25.7g) in glacial acetic acid (150cm^3) maintained at 65-70°. The mixture was stirred at 65-70° for 1 hour, filtered and evaporated to near dryness at reduced pressure. 2M NH_3 (250cm^3) was added and the mixture extracted with CH_2Cl_2

(1x100, 2x50cm^3). The extracts were chilled to 5° and then stirred with ice cold 2M HCl whereupon the hydrochloride of the required amine precipitated. White needles mp 192° ex EtOH nmr ($CDCl_3$/DMSO) 9.0-8.2 broad [3] ($-\overset{+}{N}H_3$) 7.5-7.1 complex [6] (Ar-H), 6.92 d.d J ortho = 8Hz, J meta 1-2 Hz [1] (Ar-H_6), 6.8 d J ortho = 8Hz (Ar-H_5), 5.07s [2] (Ph-CH_2-O), 3.92s [2] (Ar-CH_2-$\overset{+}{N}H_3$) 3.88s [3] (OCH_3).(Found C, 64.2, H, 6.7, Cl 12.5, N 4.9 $C_{15}H_{18}NO_2Cl$ requires C 64.3, H 6.4, Cl 12.7, N 5.0%). The hydrochloride was stirred with 2M NH_3 (100cm^3) and the free amine extracted into CH_2Cl_2 (1x100, 2x50cm^3). Evaporation of the dried (Na_2SO_4) extracts afforded the required amine as a colourless oil (45%). nmr ($CDCl_3$), 7.6-7.2 complex [5] (Ph-CH_2-O), 7.0-6.7 complex [3] (Ar-H), 5.14s [2] (Ph-CH_2-O), 3.89s [3] (OCH_3), 3.80t [2] (CH_2-NH_2), 1.54 broad s [2] removed by D_2O ($-NH_2$).

N-(3-methoxy-4-benzyloxybenzylidene)-3'-methoxy-4'-benzyloxybenzylamine (56)

3-methoxy-4-benzyloxybenzaldehyde (9g) and 3-methoxy-4-benzyloxybenzylamine (9g) were heated under partial reflux in dry benzene (150cm^3) for 6 hours. Evaporation of the solvent afforded the Schiffs base as a yellow gum which solidified on standing. ν max 1645 nmr ($CDCl_3$) 8.24s [1] (-CH=N-), 7.6-6.6 complex [16] (Ar-H), 5.16s [2] and 5.11s [2] (2xPh-CH_2-O), 4.69s [2] (Ar-CH_2-N=), 3.90s [3] and 3.86s [3] (2xOCH_3). (Found C 77.2, H 6.4, N 2.7, $C_{30}H_{29}NO_4$ requires C 77.1, H6.3, N 2.8%).

α-(3-methoxy-4-benzyloxyphenyl)-β-(3',4'-methylenedioxyphenyl) ethylamine (59)

(DMF was dried by distillation from CaH_2 prior to use).

A solution of the above Schiff's base (16g) in dry DMF ($275cm^3$) was added to a stirred slurry of NaH (2g) in dry DMF under an atmosphere of dry N_2. After stirring for 3 hours, a solution of 3,4-methylenedioxybenzyl chloride (11g) in dry DMF ($50cm^3$) was added dropwise (over 30 minutes) to the resultant wine red solution. The colour was rapidly discharged and the resultant straw coloured solution was stirred overnight. Excess NaH was destroyed by dropwise addition of MeOH ($50cm^3$) and the mixture was made acid to litmus with glacial acetic acid. The solvent was removed at 60° under reduced pressure and the residue stirred with a mixture of C_6H_6 ($250cm^3$) and 2M HCl ($250cm^3$) for 4 hours, whereupon the hydrochloride of the required amine precipitated. The hydrochloride was filtered off, washed with C_6H_6 and Et_2O and recrystallised from EtOH. Colourless needles (75%) mp 207-8°, nmr ($CDCl_3$/DMSO) 8.7 broad s [3] ($-\overset{+}{N}H_3$), 7.6-6.4 complex [11] (Ar-H), 5.88 s [2] ($-OCH_2O-$) 5.04 s [2] ($Ph-\underline{CH_2}O-$), 4.3 m [1] ($\underline{CH}-CH_2Ar$), 3.82 s [3] (OCH_3) 3.6-3.0 complex [2] ($CH\underline{CH_2}Ar$). (Found C 66.7, H 5.6 N 3.4, Cl 8.5 $C_{23}H_{23}NO_4$ requires C 66.8, H 5.8, N 3.4, Cl 8.6%). The hydrochloride was stirred with 2M NH_4OH (100ml) and the base extracted into Et_2O ($3x100cm^3$). Evaporation of the dried (Na_2SO_4) extracts afforded a quantitative yield of the free amine as a colourless oil. nmr ($CDCl_3$) 7.6-7.0 complex [5] ($\underline{Ph}CH_2O$), 7.0-6.5 complex [6] (Ar-H), 5.92 s [2]

($-OCH_2O-$), 5.14 s [2] ($PhC\underline{H}_2$)-), 4.06 d.d (J_1=9Hz and 5Hz) [1] ($-CH_2-\underline{C}HNH_2$), 3.9 s [3] (OCH_3), 2.90 d.d (J_1=5Hz and 13Hz) [1] and 2.75 d.d (J=9Hz and 13Hz) [1] ($-\underline{C}H_2CHNH_2$), 1.48 broad s [2] removed by D_2O (NH_2).

N-Carbethoxy-α-(3-methoxy-4-benzyloxyphenyl)-β-(3',4'-methylenedioxyphenyl)ethylamine (60)

The above amine (9g) was stirred with 2M NaOH ($60cm^3$) and Et_2O ($10cm^3$), then ethylchloroformate ($6cm^3$) was added dropwise. The Et_2O was allowed to evaporate and the product collected by filtration, washed with water and then recrystallised from MeOH as colourless needles (72%) mp 117-8°. nmr ($CDCl_3$) 7.52-7.24 complex [5] ($\underline{Ph}CH_2$-O), 7.0-6.4 complex [6] (Ar-H), 5.88 s [2] ($-OCH_2O-$), 5.09 s [2] ($PhC\underline{H}_2O$), 5.05-4.65 complex [2] (NH and $ArC\underline{H}NH$-), 4.04 q (J=7.5Hz) [2] ($-C\underline{H}_2CH_3$), 3.80 s [3] (OCH_3), 2.93 d (J=6Hz) [2] ($CHC\underline{H}_2$-), 1.16 t (J=7.5Hz) [3] ($-CH_2C\underline{H}_3$). (Found C 69.6, H 6.2, N 3.2, $C_{26}H_{27}NO_6$ requires C 69.5, H 6.0, N 3.1%).

N-Methyl-α-(3-methoxy-4-benzyloxyphenyl)-β-(3',4'-methylenedioxyphenyl)ethylamine (61)

The above carbamate (10g) in dry dioxan ($50cm^3$) was added dropwise to a stirred suspension of L.A.H. (5g) in boiling dioxan ($300cm^3$). After stirring under reflux for 3 hours the excess reagent was decomposed with 20% NaOH aq ($25cm^3$) and the mixture filtered. The solvent was removed under reduced pressure and the residual oil treated with 2M NaOH ($50cm^3$) and extracted with Et_2O (2x100, 1x50cm^3). The combined extracts were dried (Na_2SO_4) and treated with HCl gas, whereupon the hydrochloride of the required amine

precipitated. The product was collected by filtration and recrystallised from EtOH as colourless needles (75%) mp 173-5° nmr ($CDCl_3$) 9.96 broad s [2] ($\overset{+}{N}\underline{H}_2$), 7.5-7.2 broad s [5] ($\underline{Ph}CH_2O$), 7.0-6.4 complex [6] (Ar-H), 5.86 s [2] ($-OCH_2O-$), 5.1 s [2] ($PhCH_2O$), 3.94 s [3] (OCH_3), 3.8-3.0 complex [3] ($-C\underline{H}_2C\underline{H}$), 2.45 broad s [3] ($-\overset{+}{N}H_2C\underline{H}_3$). (Found: C 66.6, H 6.2, N 3.4, Cl 8.3, $C_{24}H_{25}NO_4HCl$ requires: C 67.4, H 6.1, N 3.3, Cl 8.3%). The hydrochloride was stirred with 2M NH_4OH ($100cm^3$) and the free amine extracted into Et_2O (2x100, 1x50cm^3). Evaporation of the dried (Na_2SO_4) extracts afforded the required base in quantitative yield as a colourless oil λ max (ε) 237(11,600), 285(7,000) nmr ($CDCl_3$) 7.6-7.1 complex 5 ($Ph-CH_2O$), 6.9-6.4 complex [6] (Ar-H), 5.92 s [2] ($-OCH_2O-$), 5.13 s [2] ($PhC\underline{H}_2O-$), 3.88 s [3] (OCH_3), 3.64t (J = 7Hz) [1] ($-CH_2C\underline{H}$), 2.78 d (J = 7Hz) [2] ($-\underline{CH}_2-CH$), 2.2 s [3] ($NHC\underline{H}_3$), 1.55 broad s [1] ($-N\underline{H}CH_3$).

Resolution of (61)

The racemic amine (61) (9.8g, 0.025 mole) and (+)-dibenzoyltartaric acid (4.71g, 0.0125 mole) were dissolved in 95% EtOH ($150cm^3$) at reflux. The solution was diluted to $350cm^3$ with hot EtOH, filtered while hot, then left to stand at room temperature. After 72 hours the crystallised solid was collected by filtration and recrystallised twice from EtOH (38%). Examination of the nmr spectrum of this salt showed the ratio of the integral over the ortho protons of the benzoyl functions (8.13 s and 8.06 s) to the integral over the benzyloxy CH_2 protons (5.0 s) to be 1:1 and thus

confirmed the disalt (63). Further confirmation for the disalt was obtained by quantitative regeneration of the free amine. Treatment of the salt with $^{M}/_{10}$ NH_4OH followed by extraction with Et_2O afforded the free amine with $[\alpha]_D^{20}$ + 72.6°. The salt was reformed and further recrystallised until the regenerated amine showed a constant specific rotation. The yield of (+)(61) was 1.5g (31%) with $[\alpha]_D^{20}$ + 87.3° (6.2% in EtOH).

(+)-N-Methyl-N-[α-(3-methoxy-4-benzyloxyphenyl)-β-(3`,4`-methylenedioxyphenyl)ethyl]aminoacetaldehyde-diethylacetal (62)

Bromoacetal (1.5g) was added portionwise over 12 hours to a stirred mixture of the (+)-amine (61) (0.5g) and anhydrous K_2CO_3 (0.3g) in dry DMF (10cm^3) at 100° under an atmosphere of dry N_2. Examination of the reaction mixture by GC (OV1/280°) showed that no further reaction occurred after 36 hours at 100°. The mixture was allowed to cool and then poured into H_2O (75cm^3). The product was extracted with C_6H_6 (4x25cm^3) and the combined extracts washed with H_2O (5x10cm^3) and evaporated. Excess bromoacetal was removed at 60° (1mm) over 30 minutes and the resultant black gum subjected to column chromatography (Al_2O_3/20%$CHCl_3$-C_6H_6) to afford the required acetal as a colourless oil (68%) $[\alpha]_D^{20}$ + 67.3° (1.4% in EtOH). nmr ($CDCl_3$), 7.5-7.2 complex [5] ($\underline{Ph}CH_2O$-), 6.9-6.3 complex [6] (Ar-H), 5.82 s [2] (OCH_2O-), 5.08 s [2] ($PhC\underline{H}_2O$), 4.46 t (J = 5Hz) [1] ($-CH_2\underline{CH}(OEt)_2$), 3.82 s [3] ($OCH_3$), 3.8-2.4 complex [9] ($2xO\underline{CH}_2CH_3$ and $Ar\underline{CH}_2\underline{CH}N\underline{CH}_2$), 2.3 s [3] ($NCH_3$), 1.15 t (J = 8Hz)

[6] (2x$\underline{CH}_3CH_2O$).

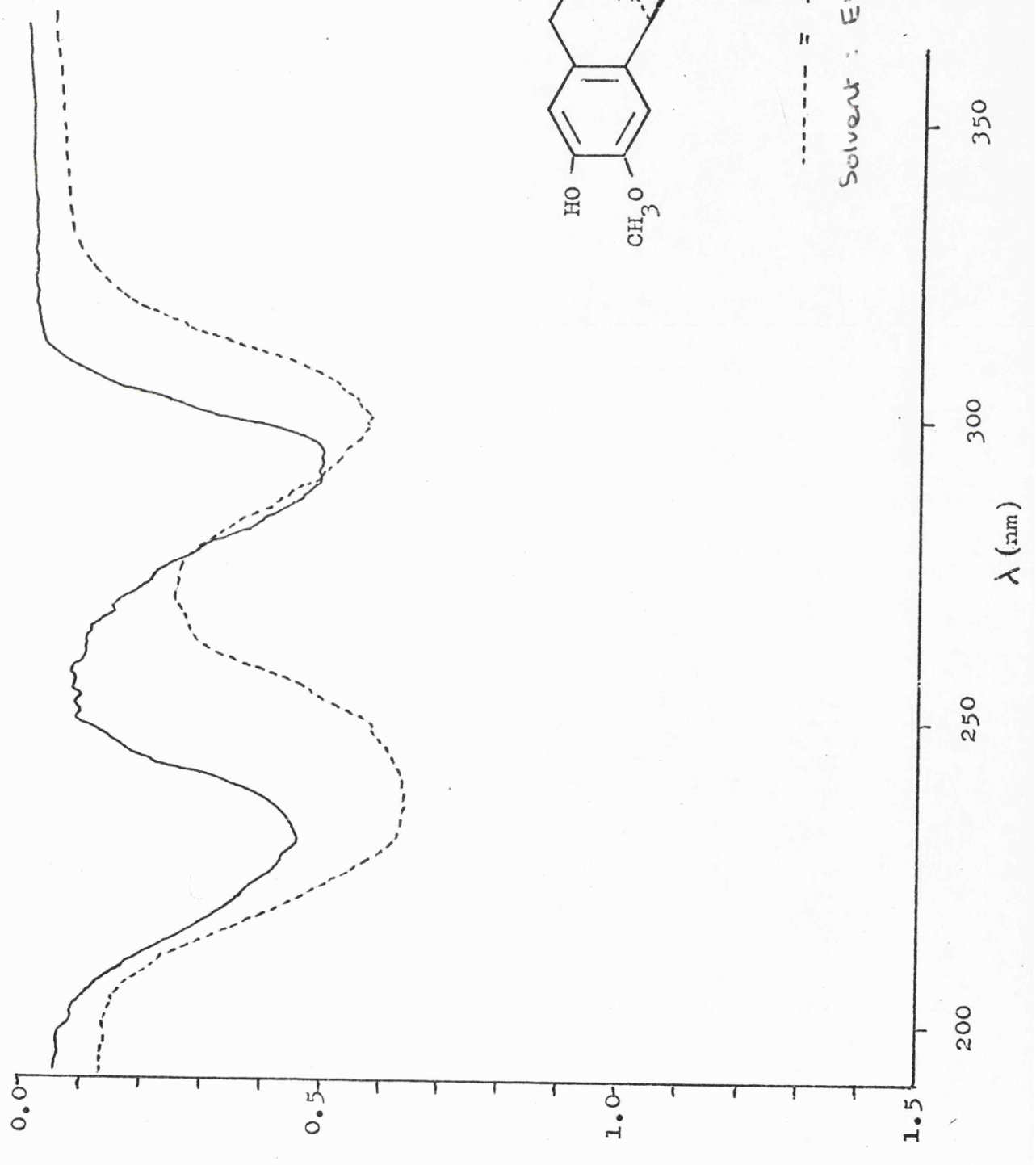
Caryachine (64) and Reframoline (65)

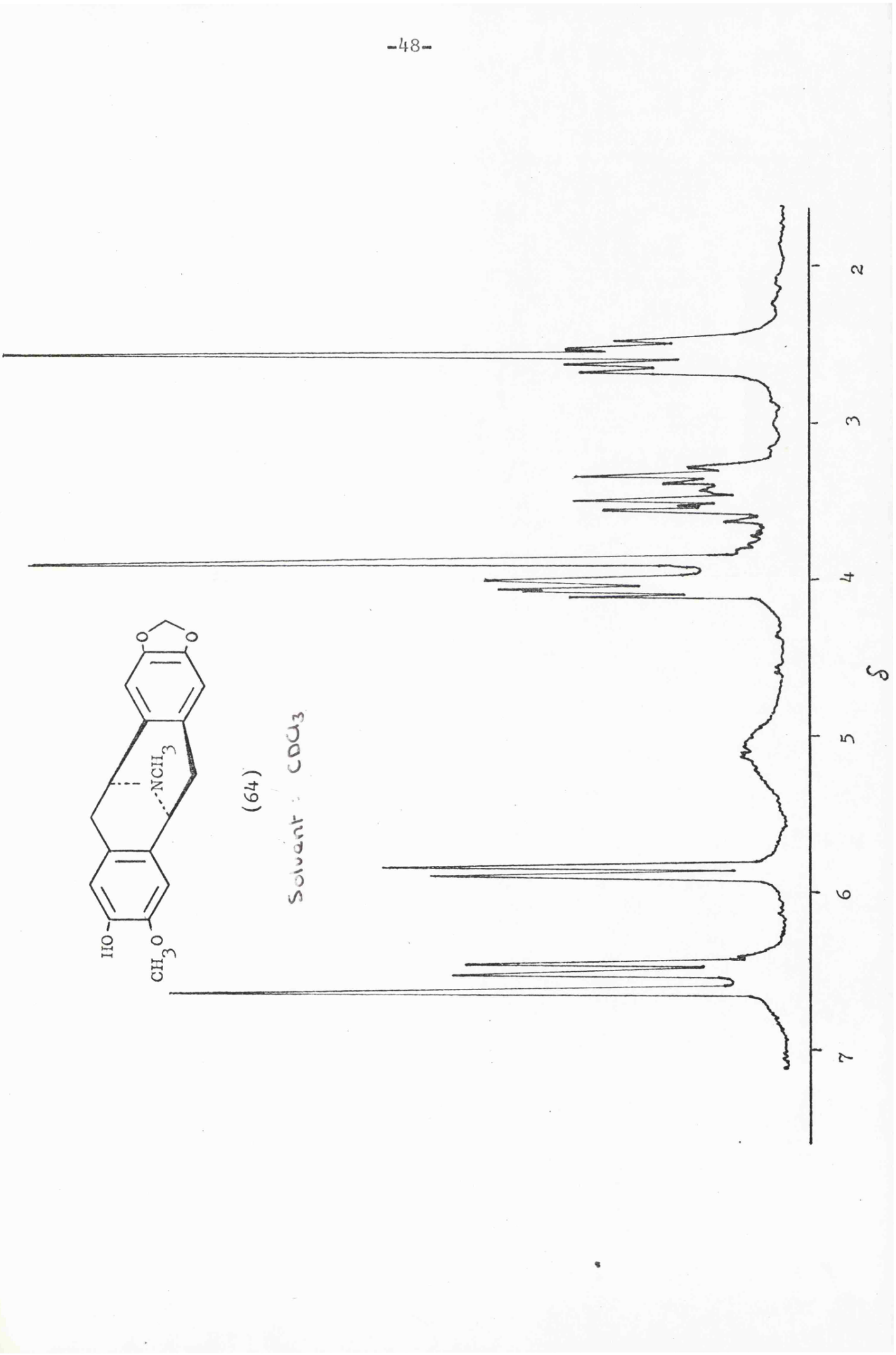
The aminoacetal (+)-(62) (400mg) was dissolved in EtOH (25cm^3) and C HCl (25cm^3) added. After standing overnight at room temperature the mixture was heated on a steam bath for 6 hours and then poured into H_2O (100cm^3). The solution was washed with Et_2O (2x50cm^3), the pH adjusted to 9 ($NaHCO_3$) and extracted with $CHCl_3$ (3x100cm^3). Evaporation of the dried (Na_2SO_4) extracts afforded a yellow oil (170mg) which solidified on trituration with Et_2O. TLC (SiO_2/10%CH_3OH-$CHCl_3$) showed two major components with Rf 0.40 and 0.15 which were separated by column chromatography (SiO_2/$CHCl_3$) to give (64) and (65) respectively. (64) was obtained as a beige crystalline solid on trituration with Et_2O (35mg, 14%) mp 170° (lit[64] mp 175°) with $[\alpha]_D^{20}$ -251° (0.43% in EtOH) (lit[64] $[\alpha]_D^{20}$ -270 in MeOH). λ max (ε) 230(7,200), 293(8,000). On addition of NaOH λ max (ε) 234(10,000), 300(9,400). λ max (hexane) resolved into 278, 285, 290, 295, 303. nmr ($CDCl_3$) 6.60 s [2], 6.50 s [1], and 6.43 s [1] (Ar-H). 5.87 s [1] and 5.82 s [1] (-OCH_2O-), 5.1 broad s [1] removed by D_2O(OH), 3.86 s [3] (OCH_3), 2.53 s [3] (NCH_3) 4.1-2.4 complex [6] (aliphatic H) mass m/e 326 (M^++1) [11%], 325 (M^+) [51%], 324 (M^+-1) [40%], 282 [2%], 190 [89%], 188 [100%]. High resolution M^+-1 found: 324.1228, $C_{19}H_{18}NO_4$ requires 324.1236.

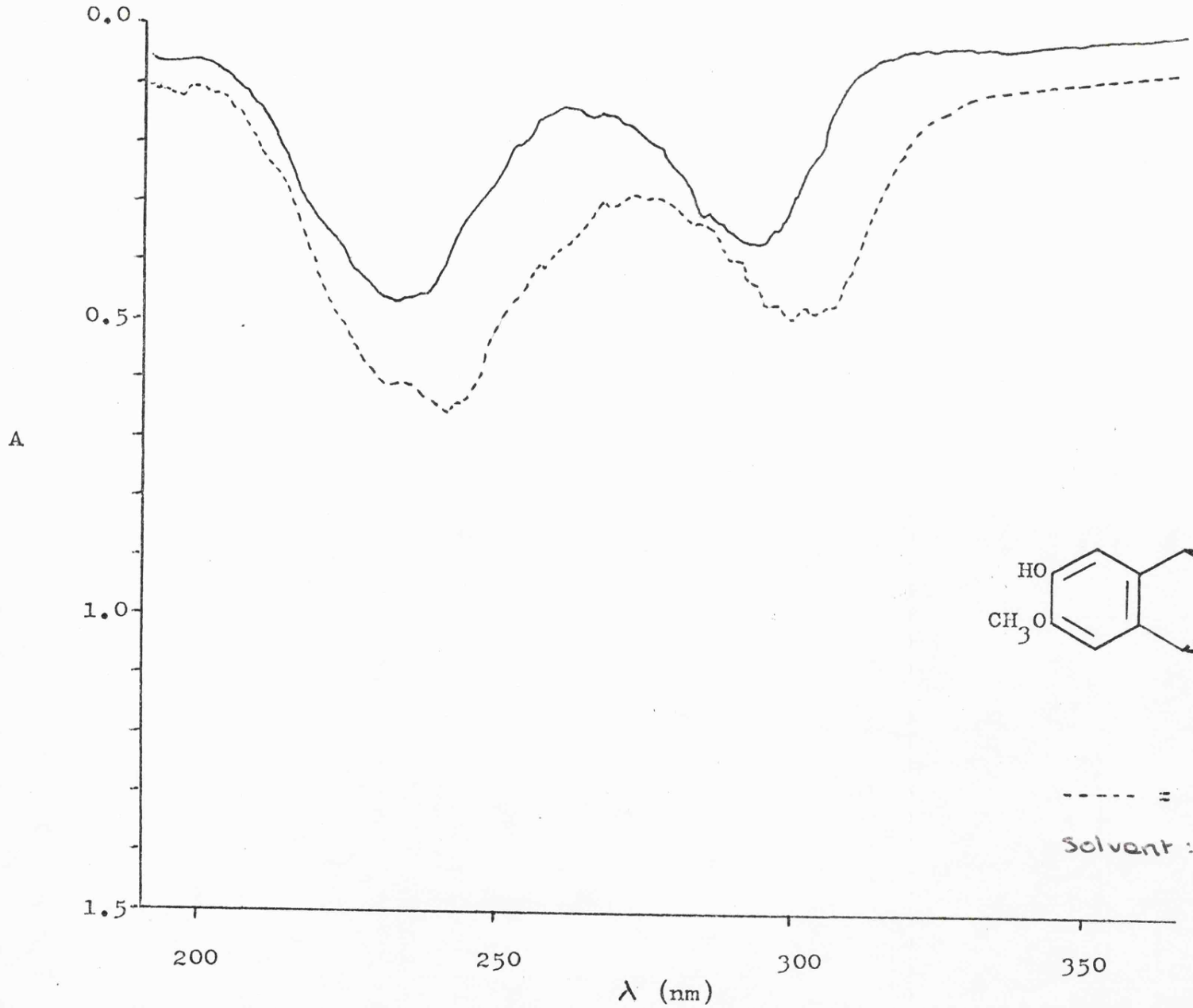
The isopavinane (65) was isolated as a beige crystalline solid on trituration with Et_2O (41mg 16%) mp 160° with $[\alpha]_D^{20}$ -144° (0.37% in EtOH) (lit[6] $[\alpha]_D^{20}$ -140° in MeOH)

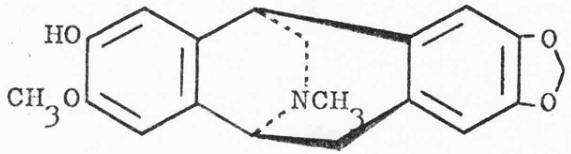
λ max (ε) 231 (7,300), 293 (6,000). On addition of NaOH λ max (ε) 242 (10,200), 300 (7,800). nmr ($CDCl_3$) 6.78 s [1] 6.73 s [1] 6.62 s [1] and 6.48 s [1] (Ar-H), 6.2 broad s [1] removed by D_2O (OH), 5.86 s [1] and 5.83 s [1] ($-OCH_2O-$), 4.08 broad (C_{10}-H), 3.86 s [3] (OCH_3), 3.8-3.44 complex [3] (C_{11}-H_2 and C_5-H), 2.89 m [2] (C_{13}-H_2), 2.55 s [3] (NCH_3). Mass m/e 326 (M^++1) [7%] , 325 (M^+) [32%] , 324 (M^+-1) [35%] , 282 [38%] , 190 [100%] , 188 [4%] . High resolution: M^+-1 found: 324.1231 $C_{19}H_{18}NO_4$ requires 324.1236.

SPECTRA


0.0
0.5
1.0
1.5
A
200
250
300
350
λ (nm)
HO
CH_3O
NCH_3
O
O
(64)
------ = + NaOH
Solvent : EtOH


HO
CH_3O
NCH_3
O
O
O
(64)
Solvent : $CDCl_3$
7
6
5
4
3
2
δ

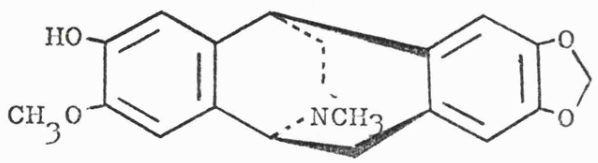




(65)

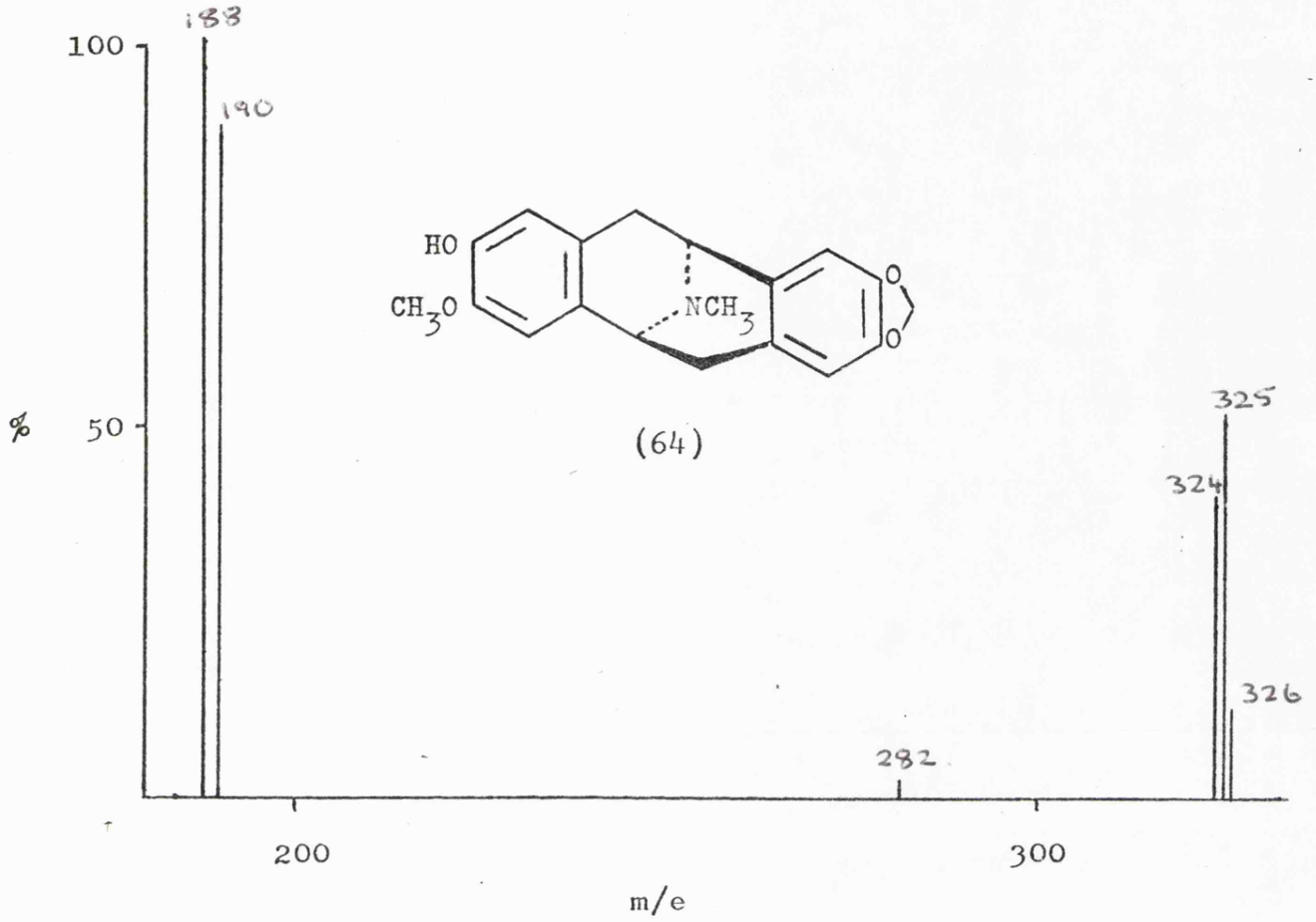
----- = + NaOH

Solvent : EtOH



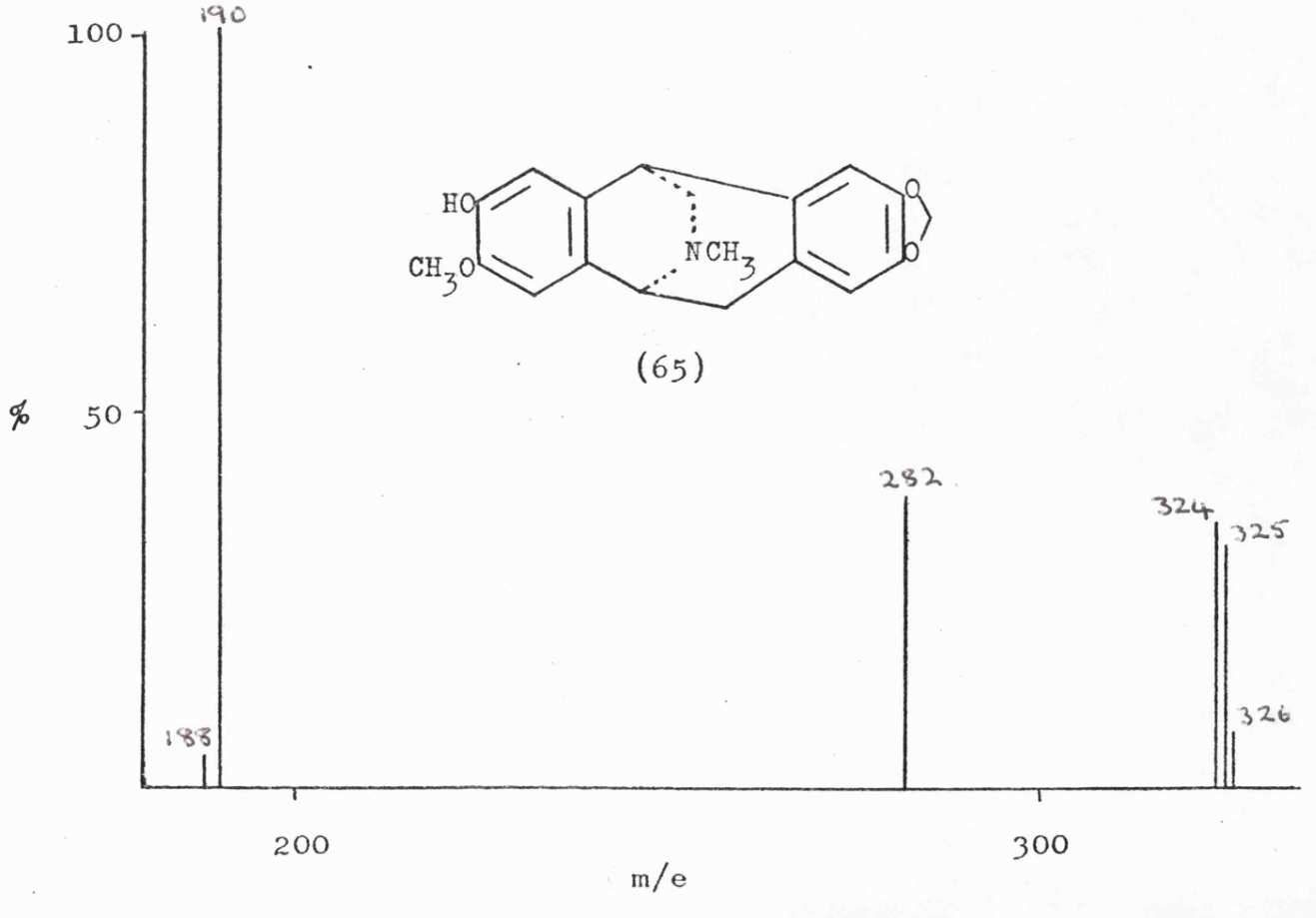
(65)

Solvent : $CDCl_3$


100
%
50
188
190
325
324
326
282
200
300
m/e

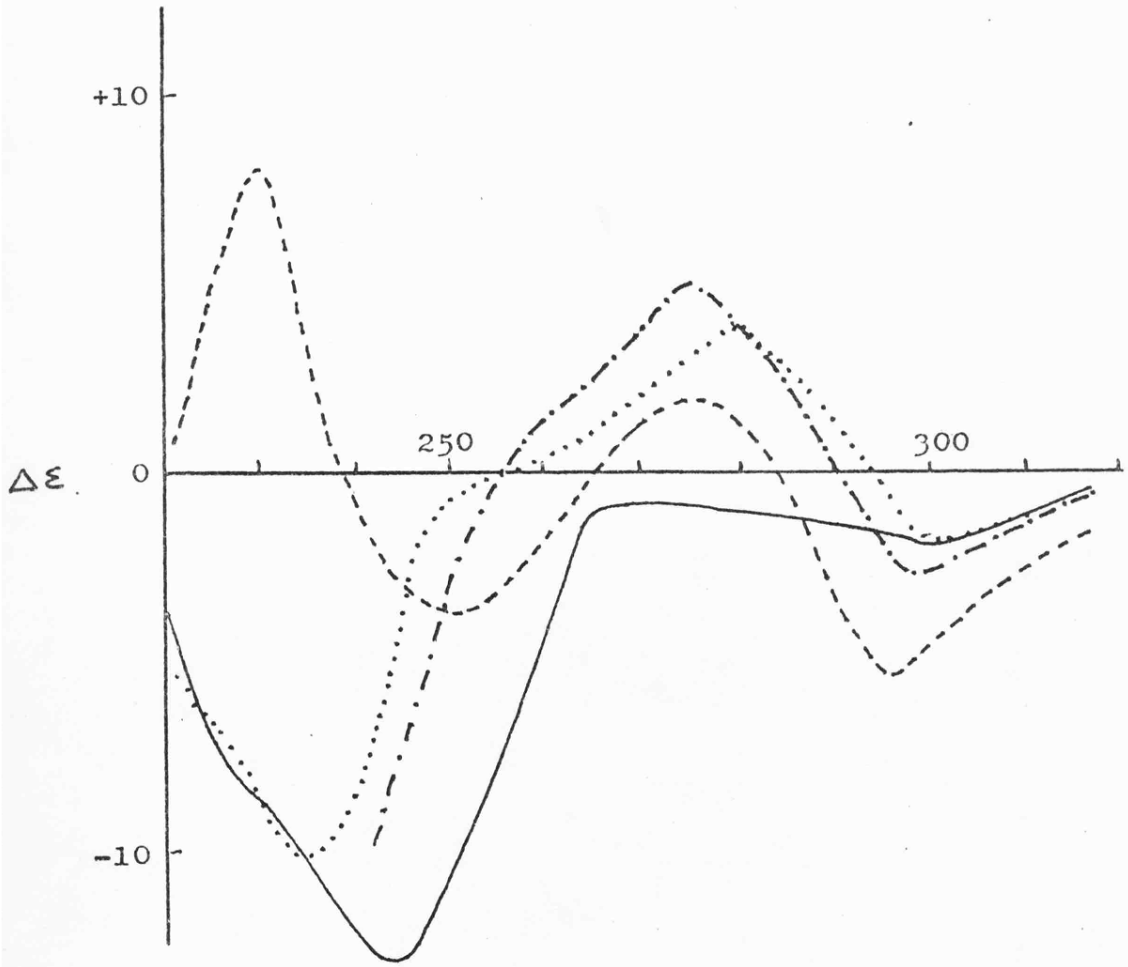
HO
CH3O
NCH3
O
O

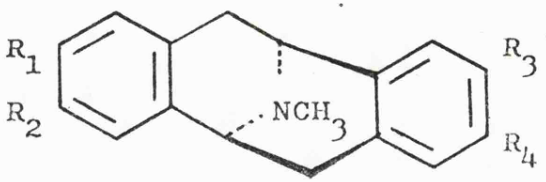
(64)


100
%
50
190
282
324
325
326
188
200
300
m/e

HO
CH3O
NCH3
O
O

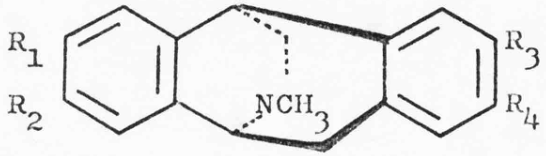
(65)





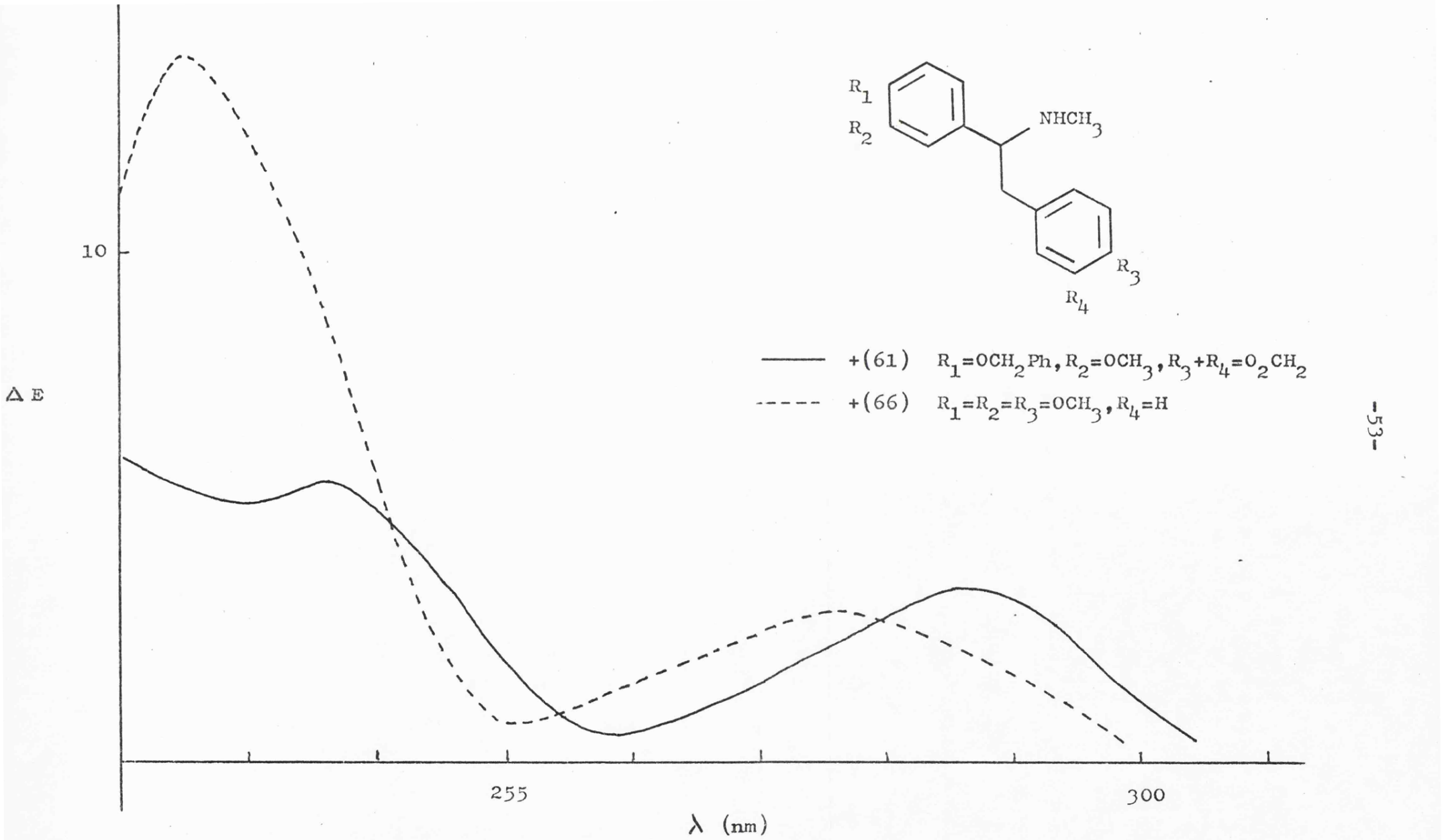
..... { (-) caryachine (64)
R_1=OH, R_2=OCH_3, R_3+R_4=O_2CH_2

-.-.-.- { (-) argemonine
R_1=R_2=R_3=R_4=OCH_3



——— { (-) reframoline (65)
R_1=OH, R_2=OCH_3, R_3+R_4=O_2CH_2

– – – – { (-) amurensine
R_1+R_2=O_2CH_2, R_3=OCH_3, R_4=OH


10
Δ E
255
300
λ (nm)
R1
R2
NHCH3
R3
R4
+(61) R1=OCH2Ph, R2=OCH3, R3+R4=O2CH2
+(66) R1=R2=R3=OCH3, R4=H

REFERENCES

1. F.L. Pyman and W.C. Reynolds, J. Chem. Soc., 97, 1320 (1910)
2. C. Schopf, Experimentia, 5, 201 (1949)
3. A.R. Battersby and R. Binks, J. Chem. Soc., 2888 (1955)
4. A.R. Battersby and D.A. Yeowell, J. Chem. Soc., 1988 (1958)
5. F. Santavy in The Alkaloids, (Edited by R.H.F. Manske) vol. 12, p. 333. Academic press, New York (1970)
6. J. Slavik, L. Slavikova and L. Dolejs, Coll. Czech. Chem. Commun., 31, 4286 (1966)
7. F. Santavy, L. Hruban and M. Maturova, Coll. Czech. Chem. Commun., 33, 4066 (1966)
8. S.M. Kupchan and A. Yoshitake, J. Org. Chem., 34, 1062, (1969)
9. M.M. Abdel-Monem and T.O. Soine, J. Pharm. Sci., 56, 976 (1967)
10. L. Dolejs and J. Slavik, Coll. Czech. Chem. Commun., 33, 3917 (1968)
11. L. Dolejs and V. Hanus, Coll. Czech. Chem. Commun., 33, 600 (1968)
12. Chung-Hsiung Chen and T.O. Soine, J. Pharm. Sci., 61, 55 (1972)
13. A.W.C. White PhD thesis University of Bath (1975)
14. A.C. Barker and A.R. Battersby, J. Chem. Soc.(C), 1317 (1967)
15. S.F. Mason, K. Schofield, R.J. Wells, J.S. Whitehurst and G.W. Vane, Tetrahedron Letters, 137 (1967)
16. O. Cervinka, A. Fabryova and V. Novak, Tetrahedron Letters, 5375 (1966)

17. T.O. Soine and O. Gisvold, J. Amer. Pharmaceut. Assoc., Edn, 33, 185 (1944), W. Schermerhorn and T.O. Soine Ibid 40, 19 (1951); F.R. Stermitz and J.N. Seiber Tetrahedron Letters 1177 (1966)

18. T.O. Soine and L.B. Kier, J. Pharm. Sci., 52, 1013 (1963)

19. Sheng-Teh Lu and Pi-Kuei Lau, J. Pharm. Soc. Japan., 83, 177 (1966)

20. N. Harada and K. Nakanishi, J. Am. Chem. Soc., 91, 3989 (1969)

21. N. Harada and K. Nakanishi, J. Am. Chem. Soc., 91, 5896 (1969)

22. M. Shamma and J.L. Moniot, Tetrahedron Letters, 3425 (1971)

23. D.H.R. Barton, R.H. Hesse and G.W. Kirby, J. Chem. Soc., 6379 (1965)

24. F.R. Stermitz and J.N.Sneiber, J. Org. Chem., 31, 2925 (1966)

25. A.R. Battersby, D.M. Foulkes and R. Binks, J. Chem. Soc., 3323 (1965)

26. D.W. Brown, S.F. Dyke, G. Hardy and M. Sainsbury, Tetrahedron Letters, 1515 (1969)

27. D.W. Brown, S.F. Dyke, G. Hardy and M. Sainsbury, Tetrahedron, 25, 1881 (1969)

28. S.F. Dyke and A.C. Ellis, Tetrahedron 27, 3803 (1971)

29. T. Kametani, The Chemistry of the Isoquinoline Alkaloids, Elsevier, Amsterdam (1969)

30. I. Monkovic and I.D. Spencer, Can. J. Chem., 43, 2017 (1965)

31. I. Monkovic and I.D. Spencer, J. Am. Chem. Soc., 87, 1137 (1965)

32. M. Shamma and B.S. Dudock, Tetrahedron Letters, 3825 (1965)

33. J. Kunitomo, Y. Okamoto, E. Yuge and Y. Nagai, Tetrahedron Letters, 3287 (1969)

34. I. Ribas, J. Sucras and L. Castedo, Tetrahedron Letters, 2033 (1972)

35. M.D. Glick, R.E. Cook, M.P. Cava, M. Srinivasan, J. Kunitomo and A.I. DaRocha, Chem. Commun., 1217 (1969)

36. K. Ito, H. Furukawa and H. Tanaka, Chem. Commun., 1076 (1970)

37. D.H.R. Barton, P.N. Jenkins, R. Letcher, D.A. Widdowson, E. Hough and D. Rogers, Chem. Commun., 391 (1970)

38. S. Undenfriend, W. Lovenberg and A. Sjoerdsma, Arch. Biochem. Biophys., 85, 487 (1959)

39. P. Muller and H.R. Schutte, Biochem. Physiol. Pflanz., 162, 234 (1971)

40. B. Umezawa and O. Hoshino, Heterocycles, 3, 1005 (1975)

41. S.F. Dyke, Advances in Heterocyclic Chemistry. (Edited by A.R. Katritzby and A.J. Boulton), Vol. 14, p. 279. Academic Press, New York (1972)

42. J. Knabe, W. Krause and K. Sierocks, Arch. Pharm., 303, 255 (1970)

43. R.M. Coomes, J.R. Falck, D.K. Williams and F.R. Stermitz, J. Org. Chem., 38, 1761 (1973)

44. S.F. Dyke, R.G. Kinsman and A.W.C. White, Tetrahedron, 31, 449 (1975) and refs. therein.

45. J. Knabe and R. Dorr, Arch. Pharm, 306, 784 (1973)

46. D.A. Walsh and R.E. Lyle, Tetrahedron Letters 3849 (1973)

47. F.R. Stermitz and D.K. Williams, J. Org. Chem. 38, 1761 (1973)

48. S.F. Dyke and A.C. Ellis, Tetrahedron, 28, 3999 (1972)

49. O. Hoshino, M. Taga, K. Ohyama and B. Umezawa, Heterocycles, 1, 223 (1973)

50. S.F. Dyke, A.C. Ellis, R.G. Kinsman and A.W.C. White, Tetrahedron, 30, 1193 (1974)

51. W.S. Ide and J.S. Buck, Organic Reactions, 4, 269 (1948) see also Organic Synthesis, Collective Vol II p. 156 (1943)

52. P.H. Gore in Friedal-Crafts and Related Reactions (Edited by G.A. Olah), Vol III, Part I, p. 1

53. M.S. Kharasch and O. Reinmu th, Grignard Reactions of Non-Metallic Substances, p. 890. Constable, London

54. R.L. Huang, J. Chem. Soc., 4089 (1957)

55. W.D. Ollis, K.L. Ormand and I.O. Sutherland, Ibid (c) 119 (1970)

56. R.G. Barnhardt and W.E. McEwen, J. Am. Chem. Soc., 89, 7009 (1967)

57. C.R. Hauser, H.M. Taylor and T.G. Ledford J. Am, Chem. Soc., 82, 1786 (1960), C.R. Hauser and G.F. Morris, J. Org. Chem., 26, 4740 (1961), G.F. Morris and C.R. Hauser, Ibid, 26, 4741 (1961)

58. S.F. Dyke, D.P. Gale, E.P. Tiley and A.W.C. White, Tetrahedron 31, 1219 (1975)

59. S.F. Dyke, R.G. Kinsman, P. Warren and A.W.C. White, Tetrahedron, 34, 241 (1978)

60. H.O. Bernhard and V. Snieckus, Tetrahedron, 27, 2091 (1971)

61. T. Kametani and K. Ogasawara, Chem. and Pharm. Bull.(Japan) 21, 893 (1973)

62. T. Kametani, S. Hirata and K. Ogasawara, J. Chem. Soc., Perkin I., 1466 (1973)

63. M. Nakazaki, I. Mita and N. Toshioka, Bull. Chem. Soc. Japan, 36, 161 (1963)

64. T. Sasaki, K. Kanematsu, Y. Tsuzuki and K. Tanaka, J. Med. Chem., 9, 847 (1966).

65. A.C. Ellis, PhD Thesis, University of Bath

66. Sheug-Teh Lu and Pi-Kuei Lan, Yakugaku Zasshi, 86, 177 (1966)

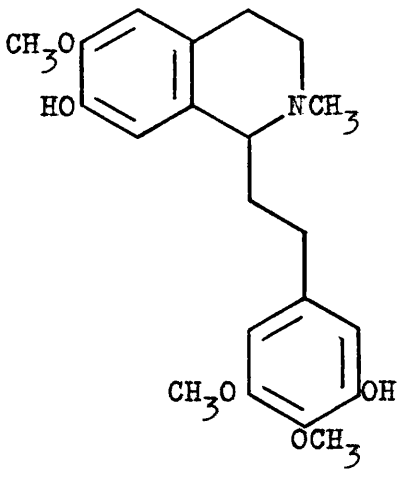
CHAPTER 2

HOMOISOPAVINANES - A HIGHLY PROBABLE PHENETHYLISOQUINOLINE ALKALOID CLASS

INTRODUCTION

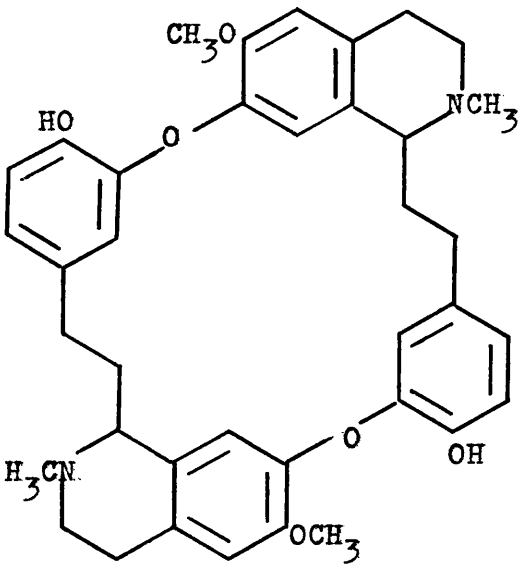
Phenethylisoquinoline alkaloids

The pavinane and isopavinane alkaloids described in the previous chapter represent two of the many classes of alkaloids which can be regarded as derivatives of 1-benzyl-tetrahydroisoquinoline. Recently, a number of alkaloids have been discovered which can be considered as derivatives of 1-phenethylisoquinoline[1-3]. These phenethylisoquinoline alkaloids can be classified into eight categories, namely: simple phenethylisoquinoline, bisphenethylisoquinoline, androcymbine, colchicine, homomorphine, homoaporphine, homoproaporphine and homoerythrina, exemplified by the structures (1) to (8) respectively.



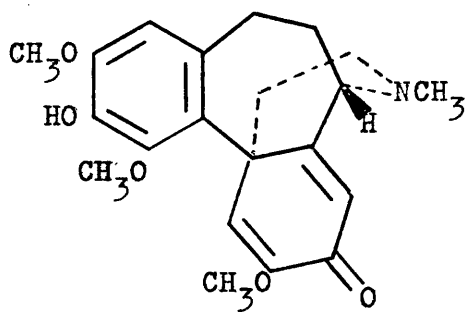
(1)

autumnaline



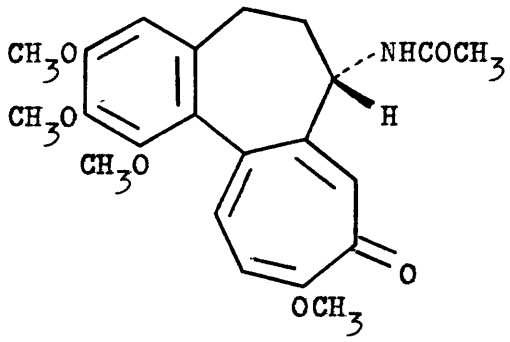
(2)

melanthioidine



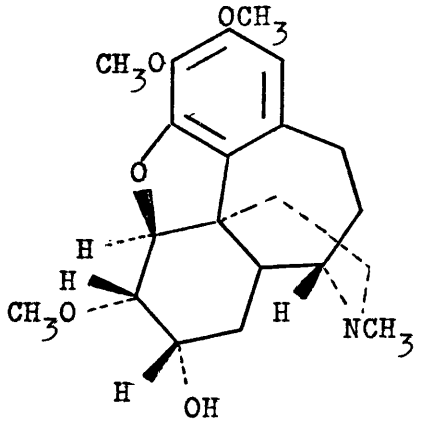
(3)

androcymbine



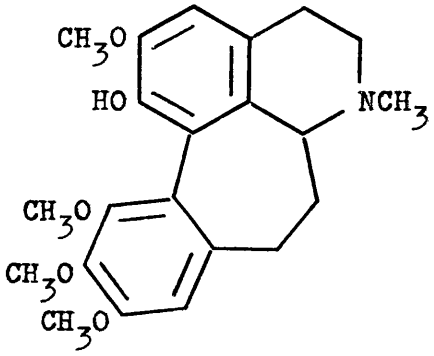
(4)

colchicine



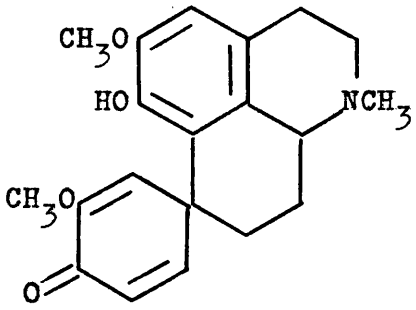
(5)

(+) kreysiginine



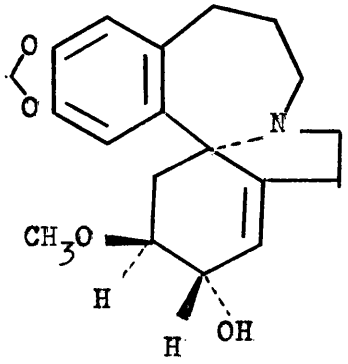
(6)

(±) kreysigine



(7)

kreysiginone



(8)

(+) schelhammerine

Occurrence

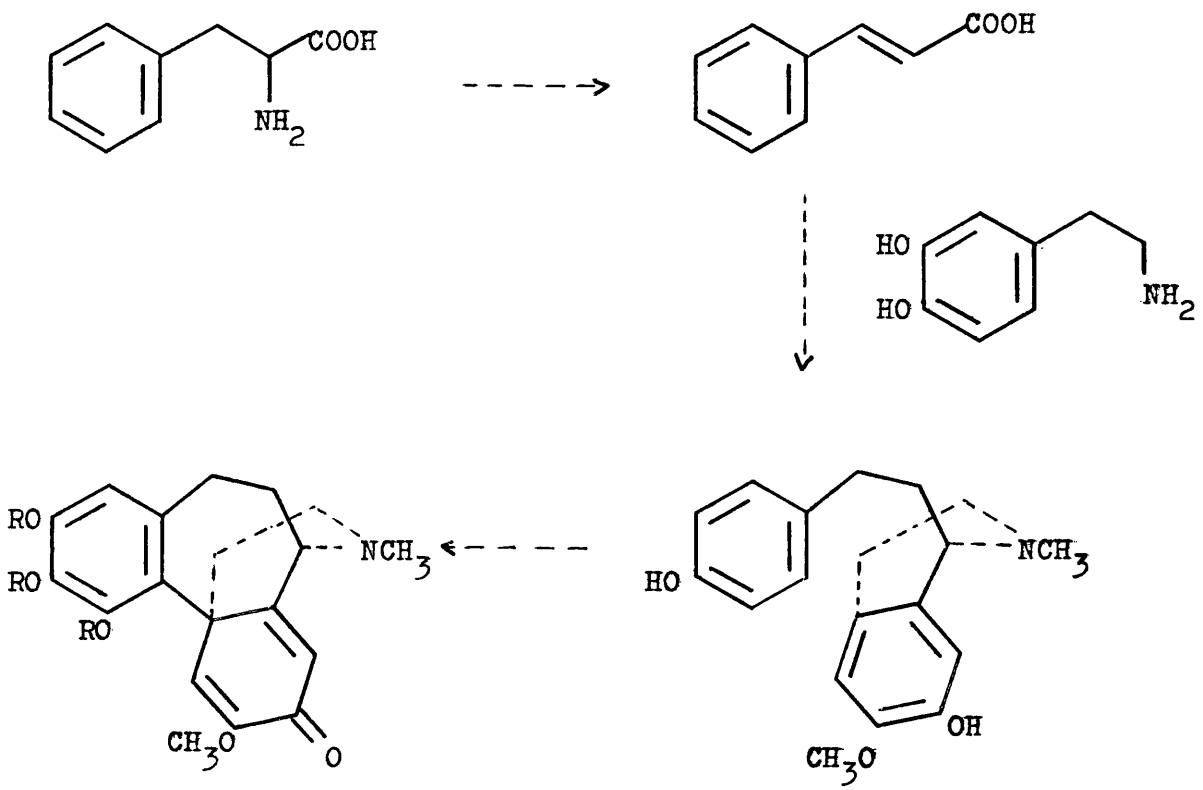
Phenethylisoquinoline alkaloids have been isolated from six plant families namely: Androcymbium, Colchicum, Kreysigia, Bulbocodium, Schelhammera and Phelline.

Biosynthesis

Although the biosynthesis of the phenethylisoquinoline alkaloids has not been extensively studied androcymbine and homoaporphines have been examined by tracer techniques. The biosynthesis of the bisphenethylisoquinoline alkaloid (-)melanthioidine probably proceeds via phenolic oxidative coupling of two molecules of diphenolic phenethylisoquinoline[4].

Androcymbine which is a precursor of colchicine, is biosynthesised from a phenethylisoquinoline. Furthermore, tyrosine is incorporated into the tropolone ring of colchicine and phenylalanine into the A ring of colchicine. It has been shown that in Colchicum autumnale Linn (Liliaceae), which produces androcymbine as well as colchicine, phenylalanine is first converted to cinnamic acid. Subsequent condensation with an amine such as dopamine affords a phenethylisoquinoline, which can become the precursor for androcymbine analogues. Scheme 1[5-9].

By analogy with the biosynthesis of aporphine alkaloids, the homoaporphines could arise either by direct intramolecular oxidative coupling of diphenolic phenethylisoquinolines or via homoproaporphines. In order to distinguish between these two possible routes Battersby et al fed labelled autumnaline (9) to Kreysigia multiflora. The total alkaloidal extracts were O-methylated to give O-methyl-



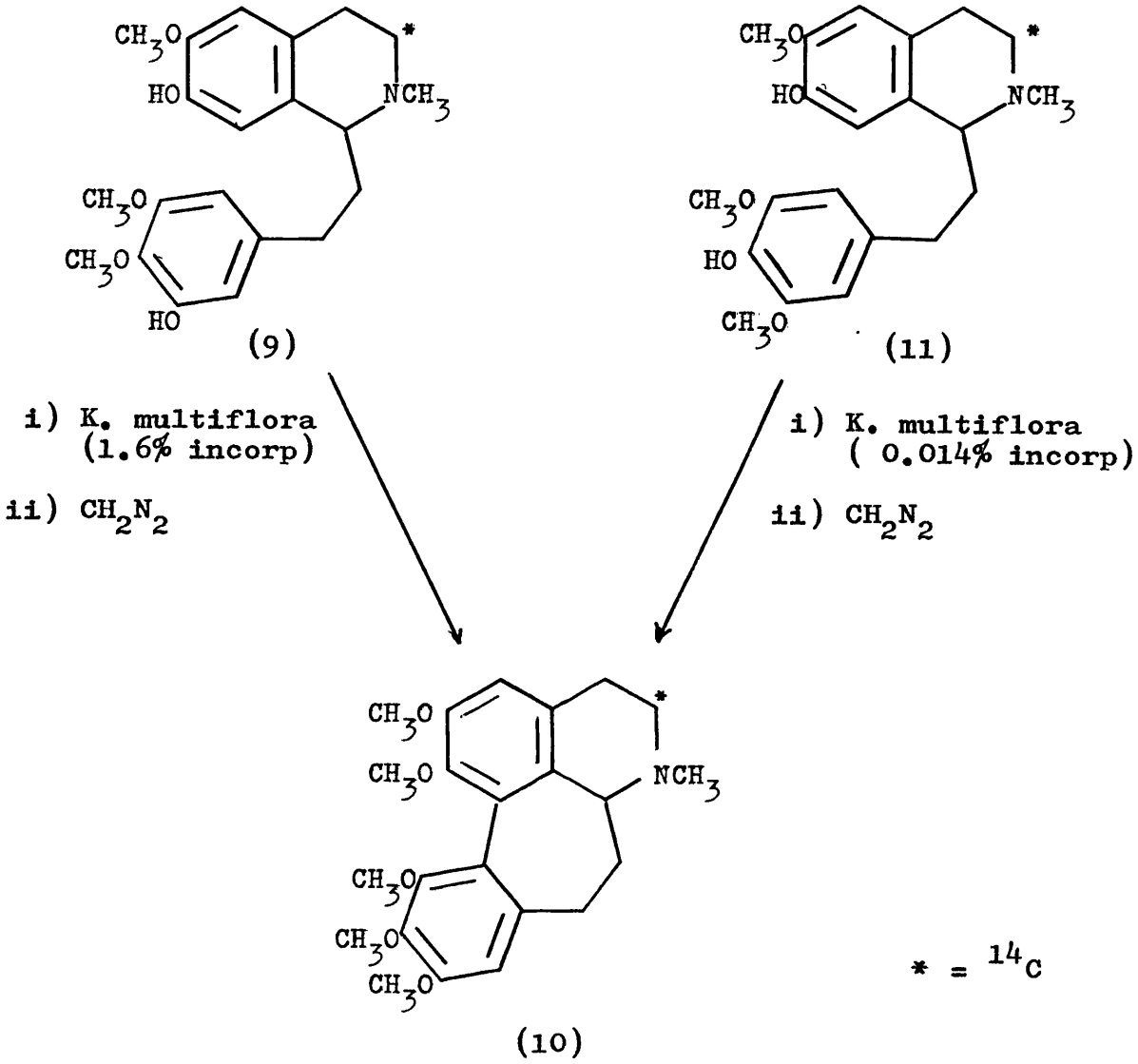
androcymbine

analogues

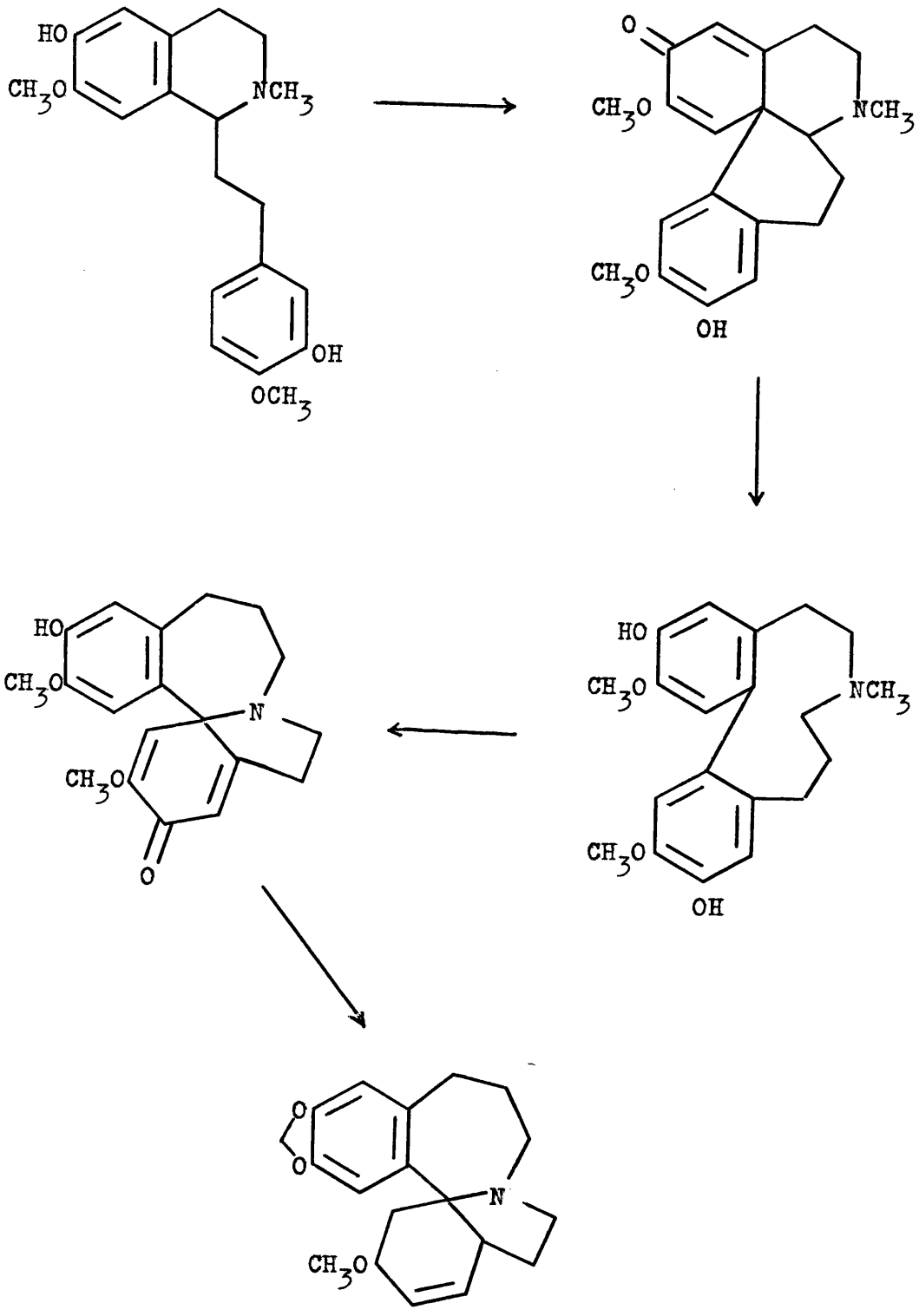
Colchicine

Scheme 1

kreysigine (10). Good incorporation was reported for autumnaline, but incorporation was poor in the case of the isomeric phenethylisoquinoline (11). Thus indicating that autumnaline is converted into homoaporphines by direct coupling without the intermediacy of homoproaporphines[10].



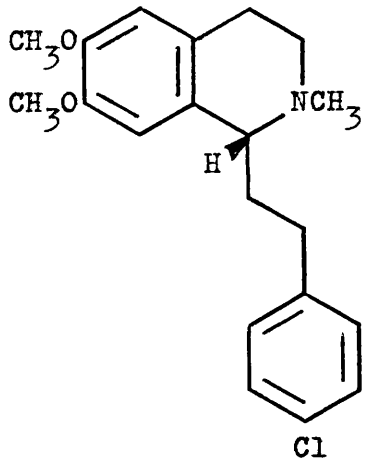
It is probable that the homoerythrina alkaloids are biosynthesised from a diphenolic phenethylisoquinoline by an analogous route to that involved in the biosynthesis of erythrina alkaloids from 1-benzyltetrahydroisoquinolines. Scheme 2.


HO
CH3O
NCH3
OH
OCH3
O
CH3O
NCH3
CH3O
OH
HO
CH3O
NCH3
CH3O
OH
HO
CH3O
N
CH3O
O
O
O
N
CH3O

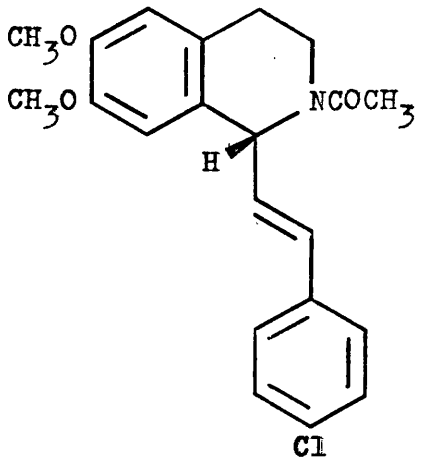
Scheme 2

Stereochemistry

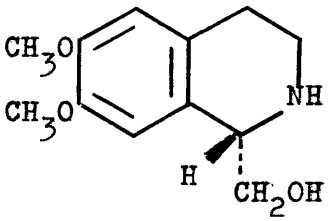
The absolute stereochemistry of the (-)-1-phenethylisoquinoline (12) was established[11] by degradation of the (-)-1-(p-chlorostyryl)-2-acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (13) with the same configuration, to (+)-calycotomine (14) of known absolute stereochemistry[12]. The o.r.d. and c.d. curves of a number of optically active phenethylisoquinolines have been recorded. When the C-1 hydrogen is beta (R-configuration), the o.r.d. curves are generally negative with minima near 240 and 290 nm[13-16].



(12)



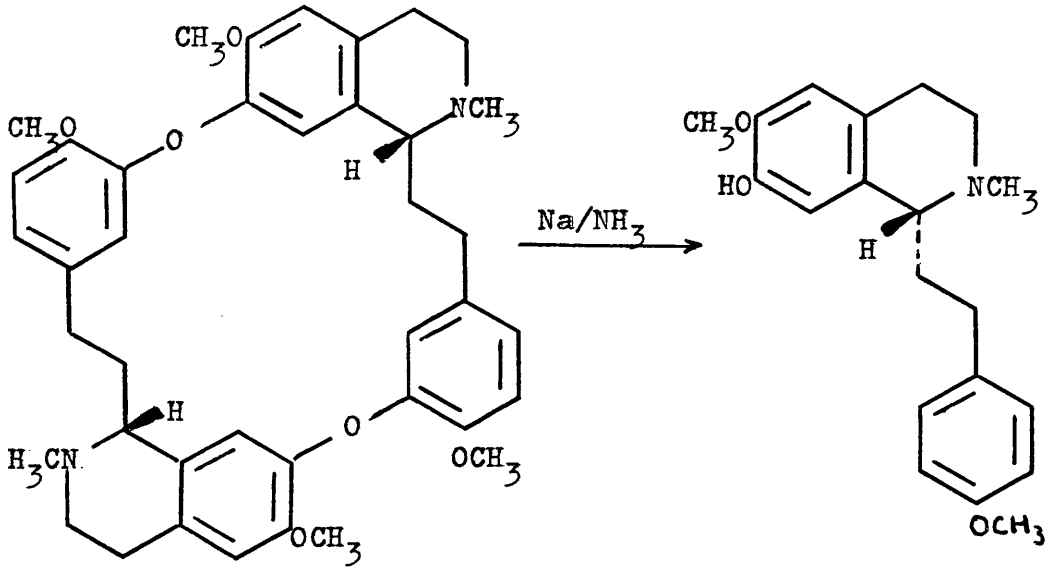
(13)



(14)

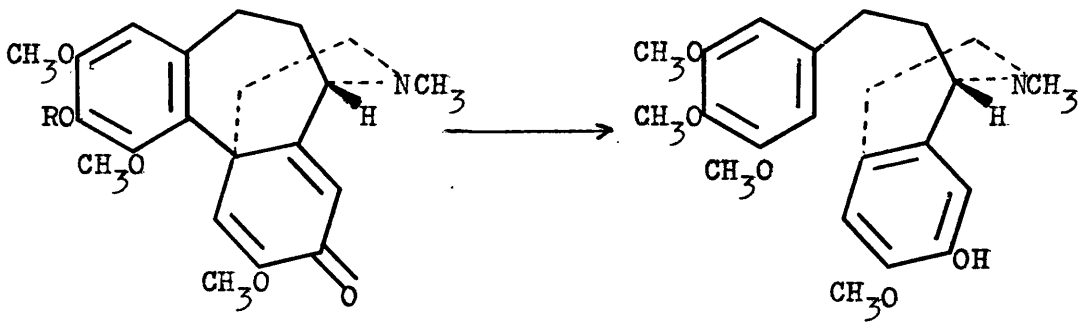
Reductive cleavage of the O,O-dimethyl derivative of melanthioidine (15) with sodium in liquid ammonia afforded the phenolic isoquinoline (16) almost exclusively. This

product showed a negative first cotton effect indicating the R configuration shown[4,17-19].



(15) (16)

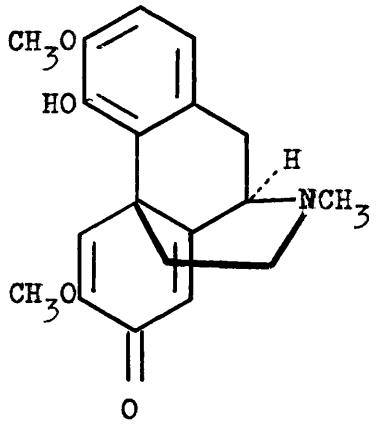
Reduction of O-methylandrocymbine (17b) with sodium in liquid ammonia yielded the phenethyltetrahydroisoquinoline (18) which showed a positive cotton effect in the 278-265 nm region, indicating the S configuration. Moreover, androcymbine and salutaridine (19) have mirror image like o.r.d. curves indicating that androcymbine must have the absolute configuration shown in figure (17a)[20].



(17a) R=H

(17b) R=CH_3

(18)

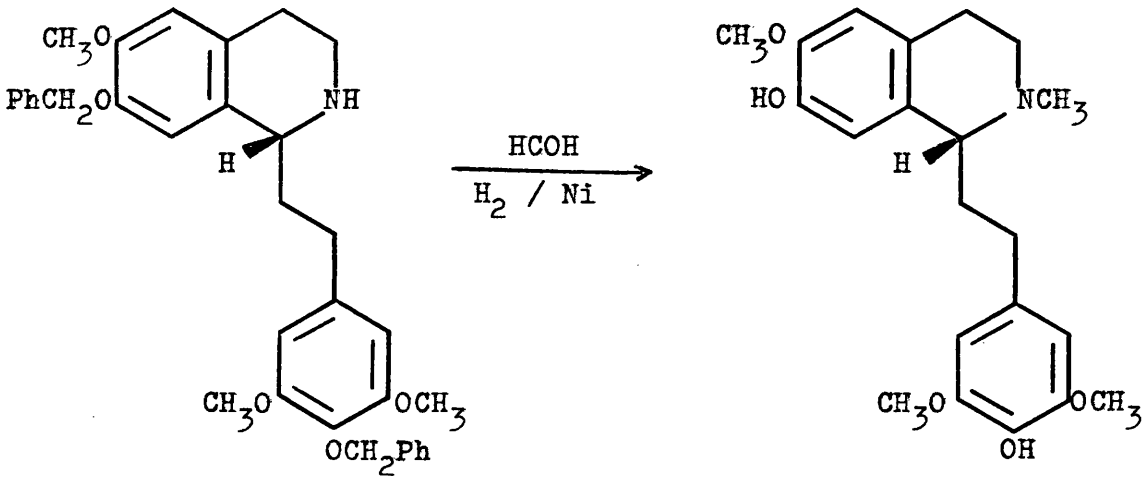


(19)

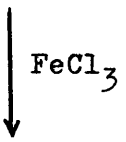
The homoaporphine alkaloids were assigned the S-configuration by comparison with a synthetic sample[14]. N-methylation and debenzylation of the dextrorotatory phenethylisoquinoline (20), afforded the laevorotatory phenolic N-methyl base (21) which upon oxidation with ferric chloride, gave the laevorotatory homoproaporphine (22). Acid catalysed dienone-phenol rearrangement then afforded (-)-multifloramine (23) identical with the natural product. Scheme 3.

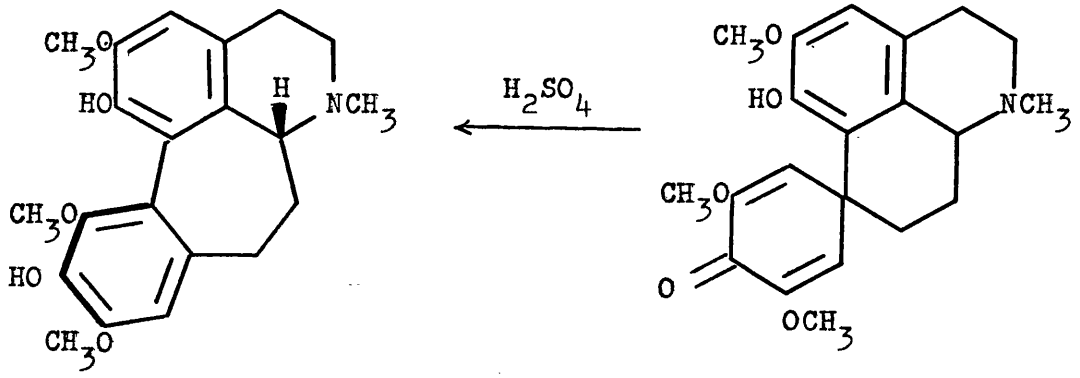
Naturally occurring (-) floramultine (24) exhibits a positive c.d. curve with a peak at 255 nm and previous studies with biphenyl systems have shown this to be associated with the absolute configuration shown[21].

The complete structure and absolute configuration (25,35,55) of the homoerythrina alkaloids was determined by X-ray analysis[22-24].



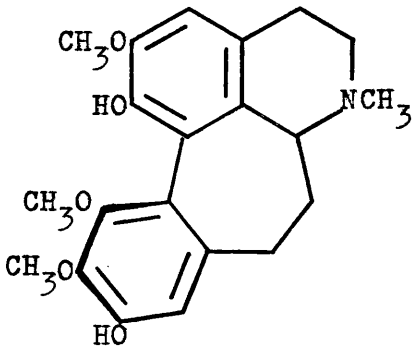
(20) (21)





(23) (22)

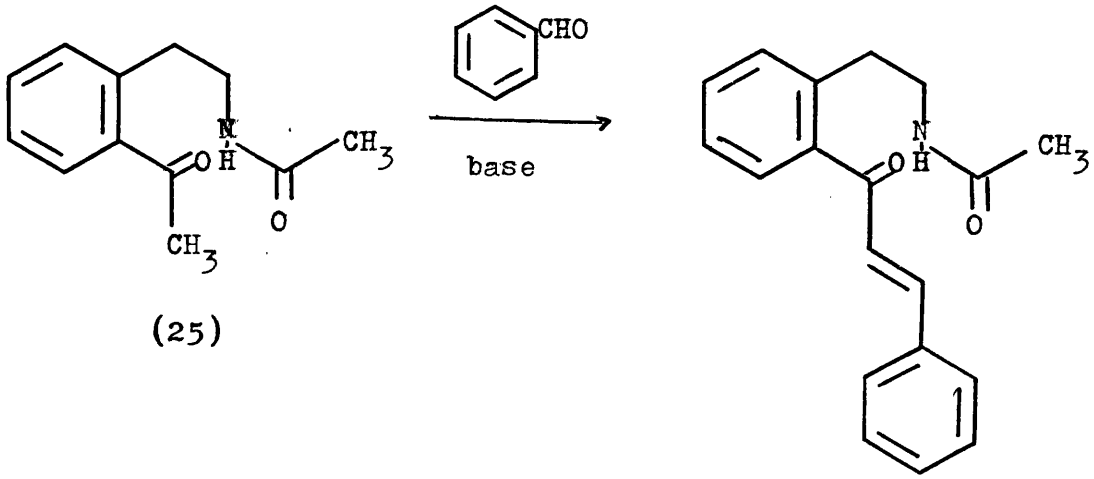
Scheme 3



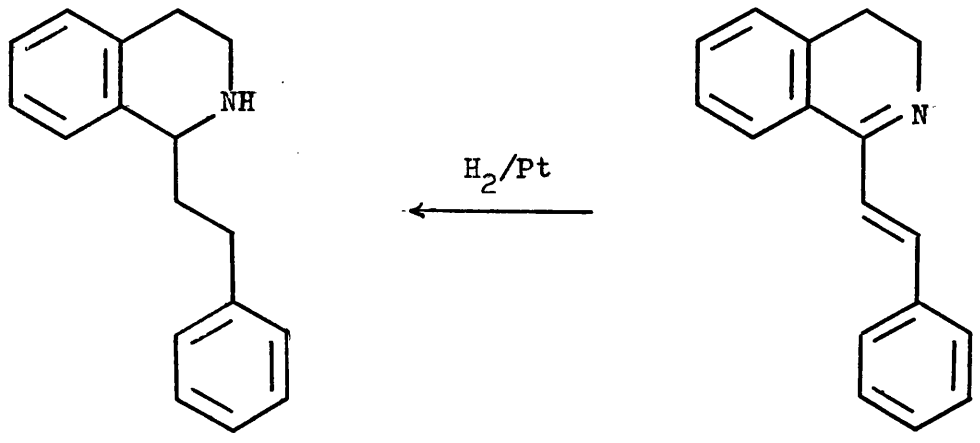
(24)

Synthesis

1-Phenethyl-1,2,3,4-tetrahydroisoquinolines can be prepared by condensation of keto amides of the type (25) with benzaldehyde derivatives to give, upon hydrolysis of the amide function, intensely coloured imines of the type (26). Catalytic reduction then affords the tetrahydroisoquinoline (27)[25-27].

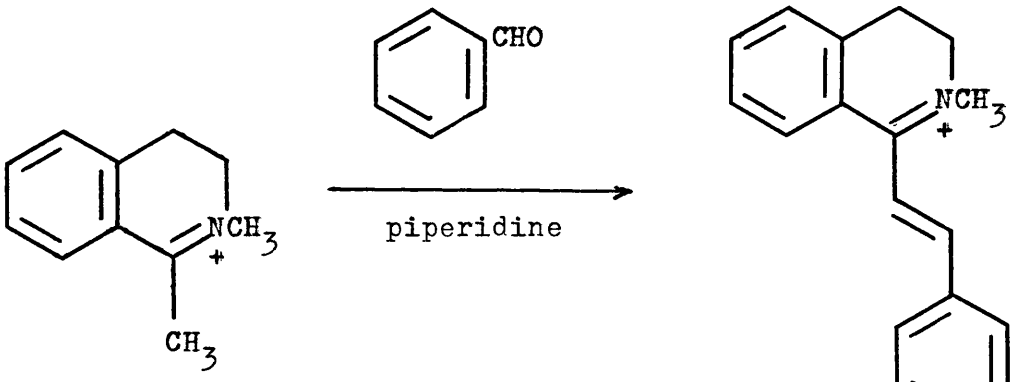


(25)



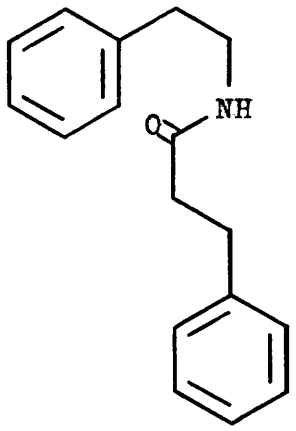
(27) (26)

Alternatively immonium salts of the type (28) which possess an activated methyl group can be condensed with benzaldehyde derivatives in the presence of a base such as piperidine. Reduction of the resultant salt (29) affords the tetrahydro base[28].



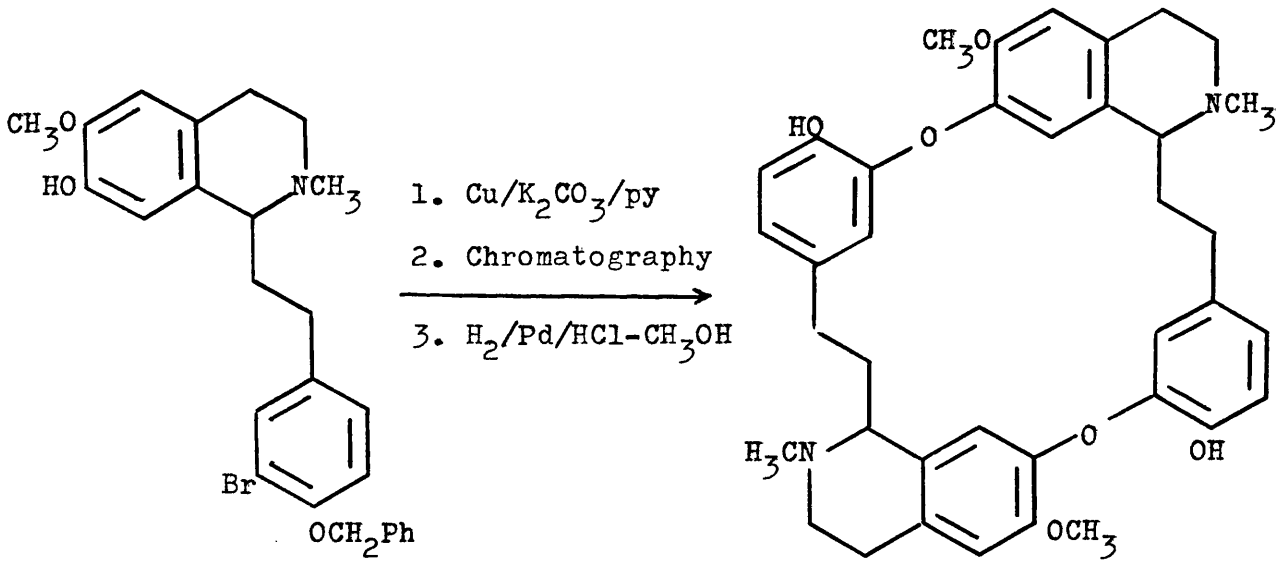
(28) (29)

The most convenient method of preparing 1-phenethyl-isoquinolines is the Bischler Napieralski cyclisation of N-acyl-2-arylethylamines of the type (30)[28].



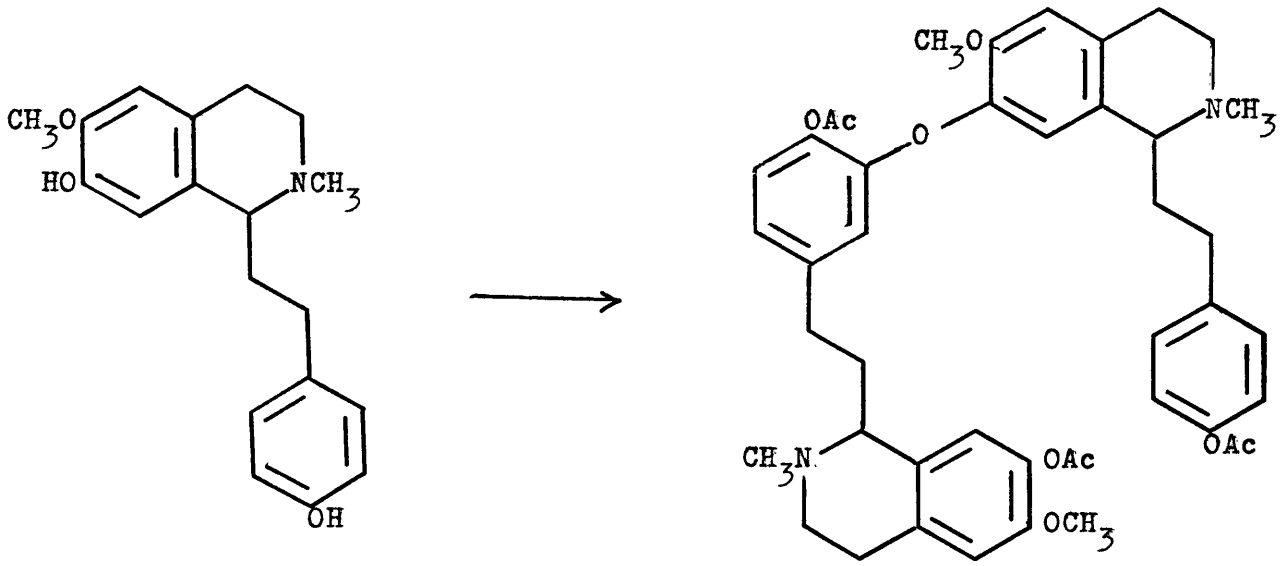
(30)

Battersby has synthesised (±) melanthioidine (32) by treating the racemic bromophenethylisoquinoline (31) under Ullmann conditions with copper powder in dry pyridine. The resultant diastereomeric dibenzylmelanthioidines were separated by chromatography and debenzylation of one of these isomers afforded (±) melanthioidine. The synthesis was repeated starting with optically active (-) (31) to afford (-) melanthioidine[4,29].



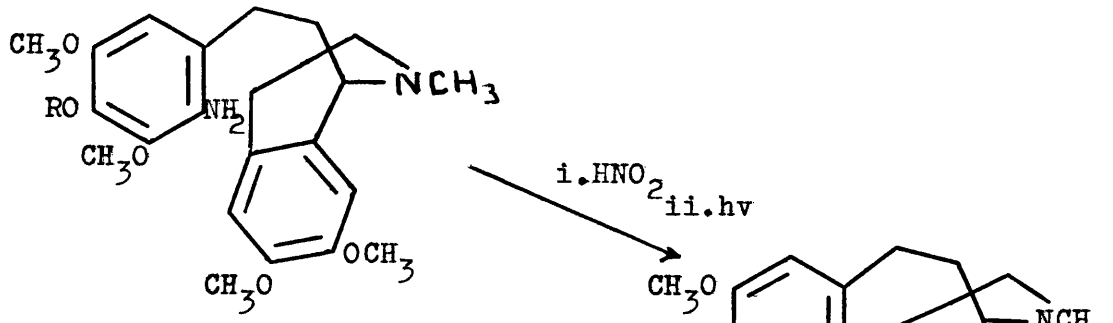
(31) (32)

In an attempt to emulate the biogenetic process leading to melanthioidine Kametani isolated the dimer (34) by treatment of the racemic phenethylisoquinoline (33) with hydrogen peroxide and homogenized potatoe peelings[29].

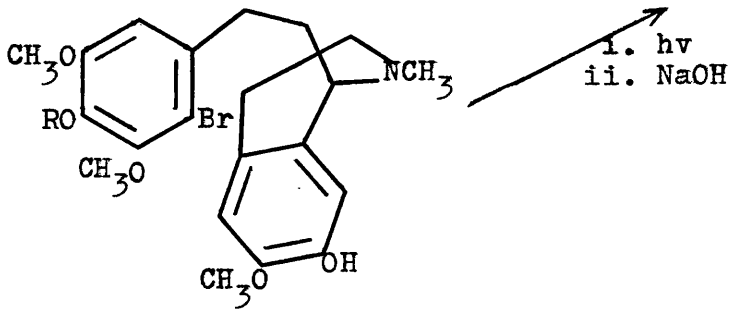


(33) (34)

(±) Androcymbine (37,R=H) and (±) O-methylandrocymbine (37,R=CH_3) have been synthesised by photo-Pschorr cyclisation of the appropriate aminoisoquinolines (35)[30] and by photolytic dehydrobromination of the appropriate 2-bromophenethylisoquinolines (36)[32,33].



(35)

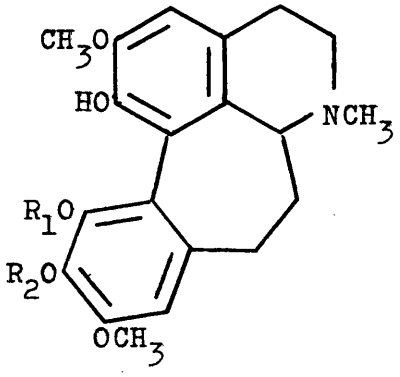


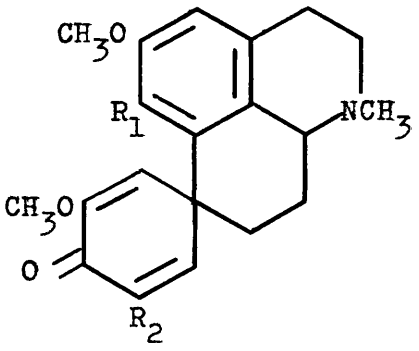
(36)

(37)

Homoaporphine alkaloids have been synthesised by intramolecular oxidative aryl-aryl coupling of both phenolic and non-phenolic isoquinolines, followed by dienone-phenol rearrangement (see chapter 3)[14,16,34-39]. Homoproaporphines have also been prepared by phenolic oxidation (see chapter 3)[16,34-42].

Multifloramine (38a), kreysigine (38b) and O-methylkreysiginone (39a) have been prepared by photolysis of the appropriate bromotetrahydrophenethylisoquinolines. In each of these syntheses the bromine was located at C-8 or C-2' of the tetrahydroisoquinoline precursor[32,33,43]. Kreysigine (38b) and the homoproaporphine (39b) were prepared by photo-Pschorr cyclisation of the appropriate aminoisoquinolines[31,44].

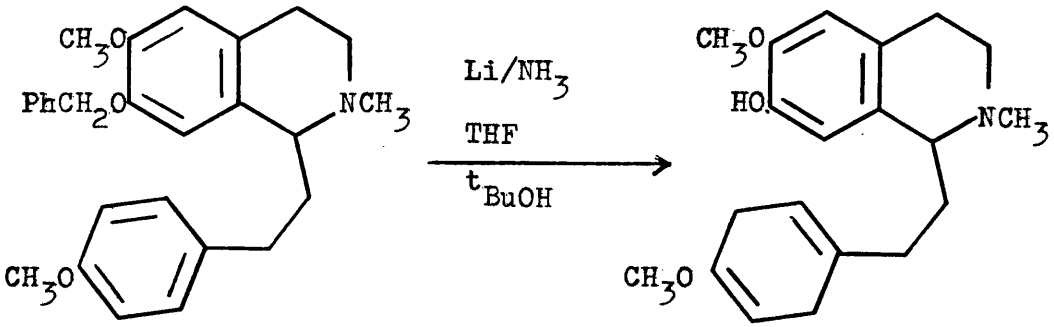




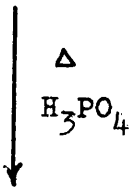
	R_1	R_2
(38a)	CH_3	H
(38b)	CH_3	CH_3

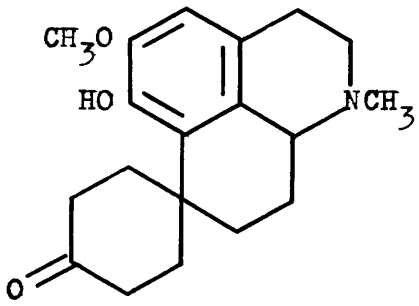
	R_1	R_2
(39a)	OCH_3	H
(39b)	OH	OCH_3

A new method for the synthesis of reduced homoproaporphines (42) involves Birch reduction of the phenethyltetrahydroisoquinoline (40), followed by treatment of the intermediate enol ether (41) with hot phosphoric acid[45].



(40) (41)



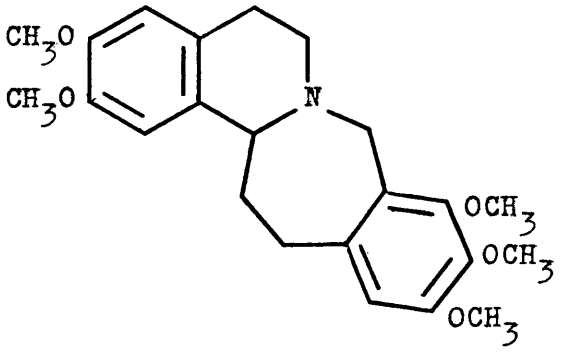


(42)

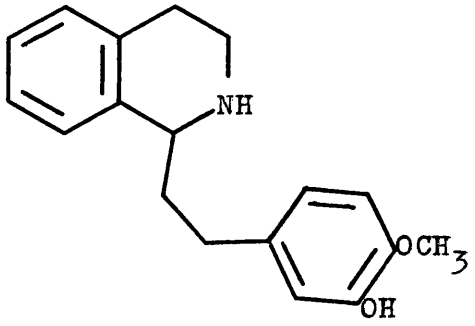
Although the homoerythrina alkaloids have not been synthesised an approach along biogenetic lines has been reported[46].

Homoprotoberberines

No naturally occurring homoprotoberberines are known although it is probable that such a species will be isolated from plant sources. Homoprotoberberines e.g. (43) have been prepared by the condensation of secondary 1-phenethyltetrahydroisoquinolines with formaldehyde[15,47,48]. The base (44) undergoes cyclisation para to the hydroxy-group with formaldehyde and acid, and ortho to the hydroxy-group in the absence of acid[49].

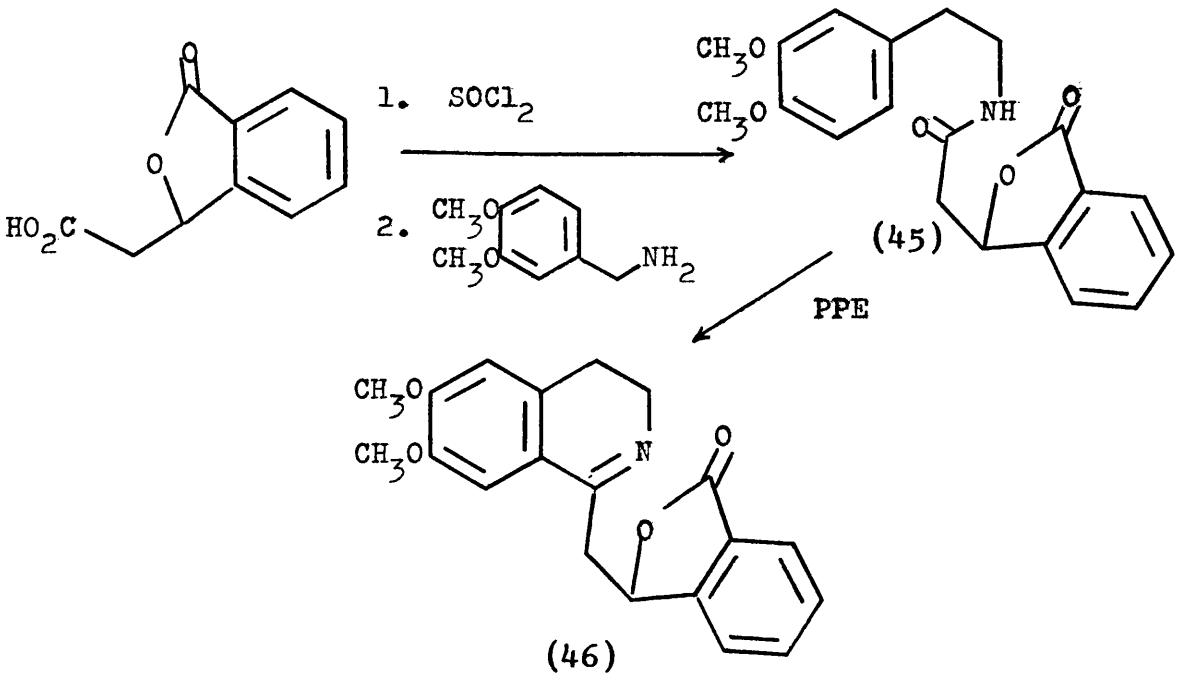


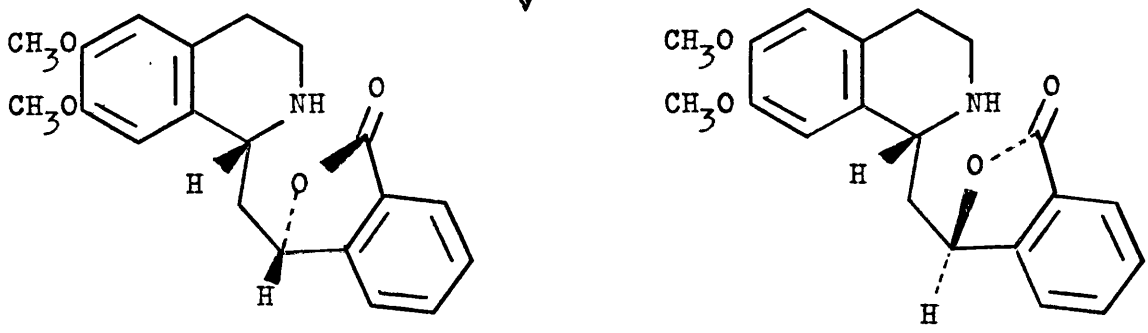
(43)



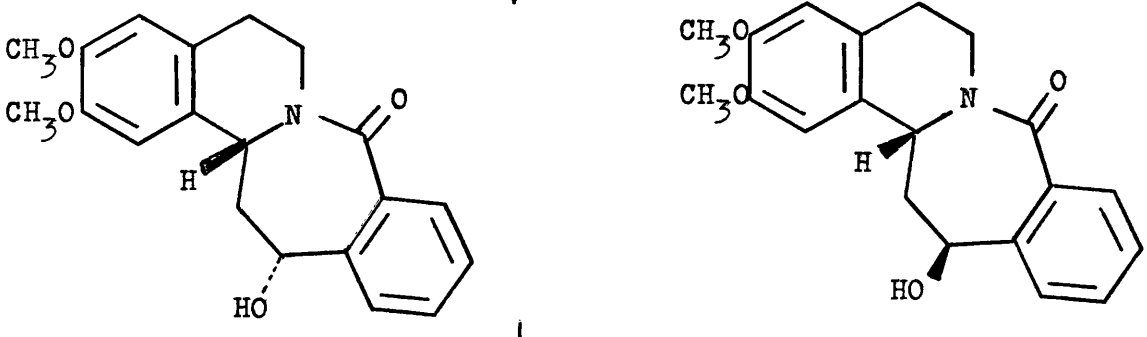
(44)

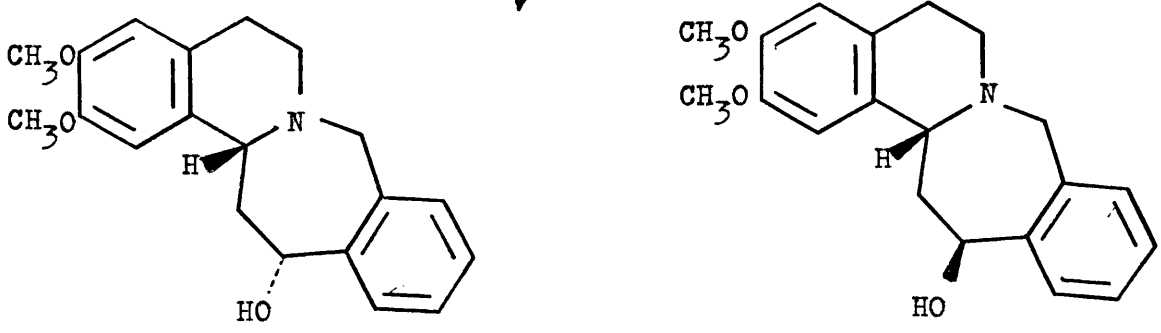
In an alternative approach[48] condensation of the acid chloride of phthalide-3-acetic acid with homoveratrylamine afforded the amide lactone (45). Bischler-Napieralski cyclisation then gave the imine (46) which, upon reduction with Adams catalyst, furnished a diastereoisomeric mixture of the homophthalideisoquinolines (47) and (48). Treatment with methanolic potassium hydroxide afforded the diastereomeric lactams (49) and (50) which were isolated in the ratio of 7:1. These lactam alcohols were individually reduced to gove the homoprotoberberines (51) and (52) respectively. Scheme 4.





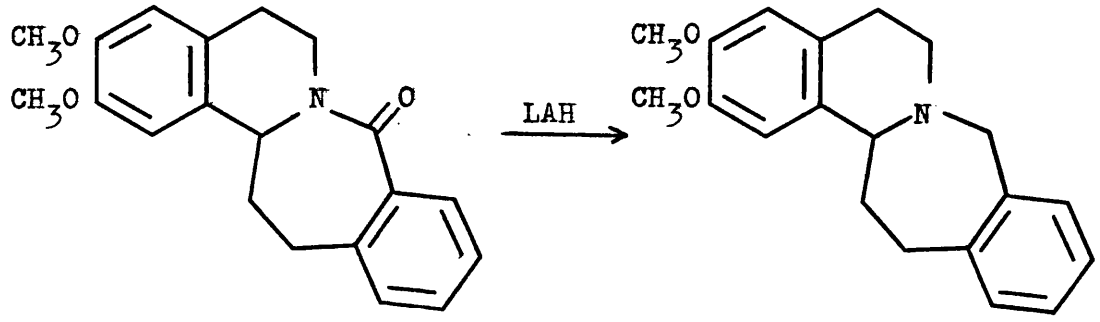
KOH/CH_3OH





Scheme 4

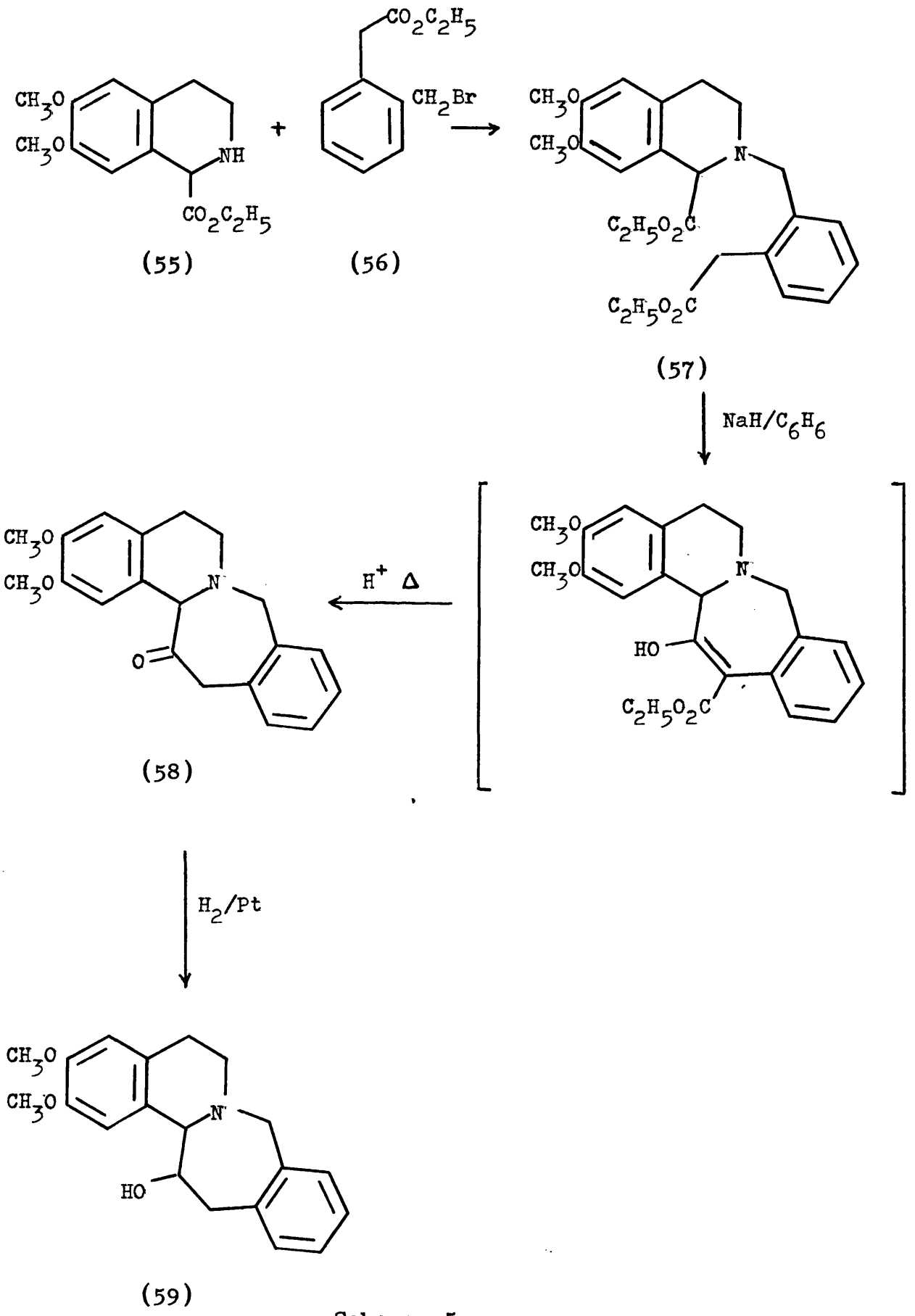
Alternatively hydrogenolysis of the lactam alcohols (49) and (50) in ethanolic perchloric acid with palladium on carbon catalyst afforded the lactam (53) which, upon reduction with lithium aluminium hydride, gave the homoprotoberberine (54).



(53) (54)

In a third approach, condensation of the amino ester (55) with ethyl-2-bromomethylphenylacetate (56) gave the diester (57). Dieckmann cyclisation followed by hydrolysis and decarboxylation afforded the amino ketone (58). Reduction with Adams catalyst then gave the 14-hydroxyhomoprotoberberine (59). Scheme 5.

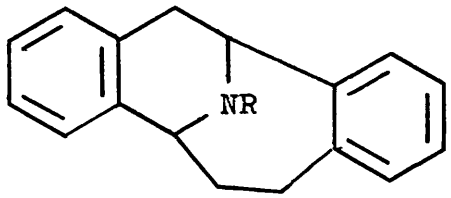
Studies of the rates of methiodide formation and the infra red and nmr spectra of the homoprotoberberines indicate, that the cis B/C ring fusion is favoured. A series of optically active homoprotoberberines have been synthesised from phenethylisoquinolines of known absolute configuration. It has been found that homoprotoberberines with the R-(+) configuration show an o.r.d. curve with a positive cotton effect centred near 247 nm[15].


CH3O
CH3O
NH
CO2C2H5
CO2C2H5
CH2Br
(55)
(56)
(57)
NaH/C6H6
H+ Δ
(58)
H2/Pt
(59)

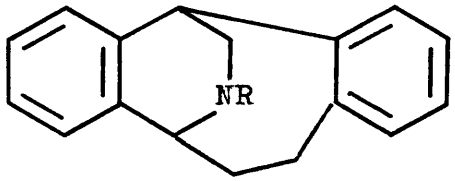
Scheme 5

Homopavinanes and Homoisopavinanes

No homopavinane or homoisopavinane alkaloids, based on the ring systems (60) and (61) respectively, have been found to occur naturally to date. However, it is the author's belief that both of these ring systems represent highly probable phenethylisoquinoline alkaloid classes.



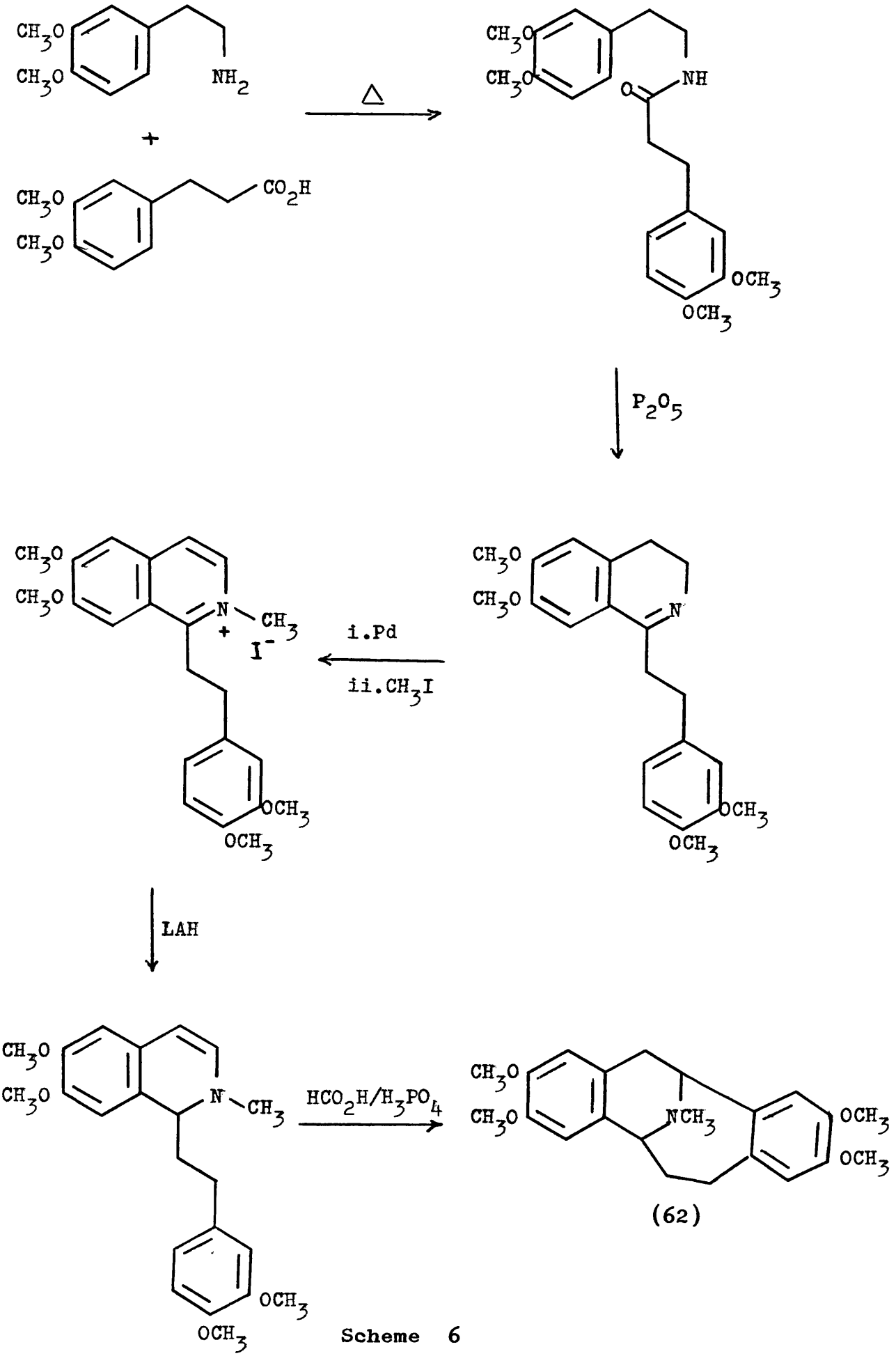
(60)



(61)

Stermitz has prepared the homopavinane (±)-homoargemonine (62) by a method analogous to that used in the preparation of the naturally occurring pavinanes[50] (see chapter 1). Scheme 6.

The discussion and experimental sections of this chapter describe the successful synthesis of compounds based on the homoisopavinane ring system. This work constitutes the first reported synthesis of compounds of this type.

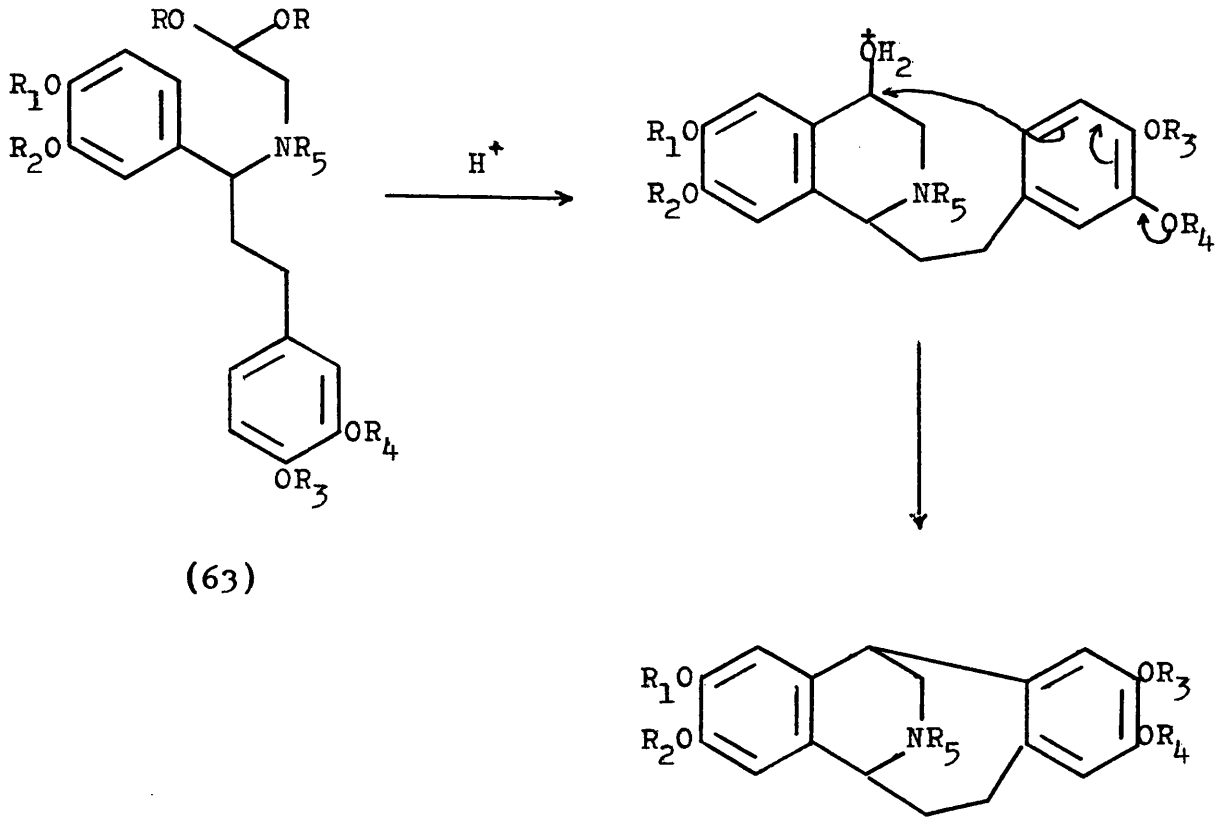

CH3O
CH3O
NH2
+
CO2H
△
NH
O
OCH3
P2O5
N
CH3
I-
i.Pd
ii.CH3I
LAH
HCO2H/H3PO4
NCH3

(62)

Scheme 6

DISCUSSION

It was decided to attempt the synthesis of the homoisopavinane system by a route analogous to that used in the preparation of isopavinanes (see chapter 1), namely, acid catalysed cyclisation of a benzylaminoacetal of the type (63). Scheme 7.



(63)

(64)

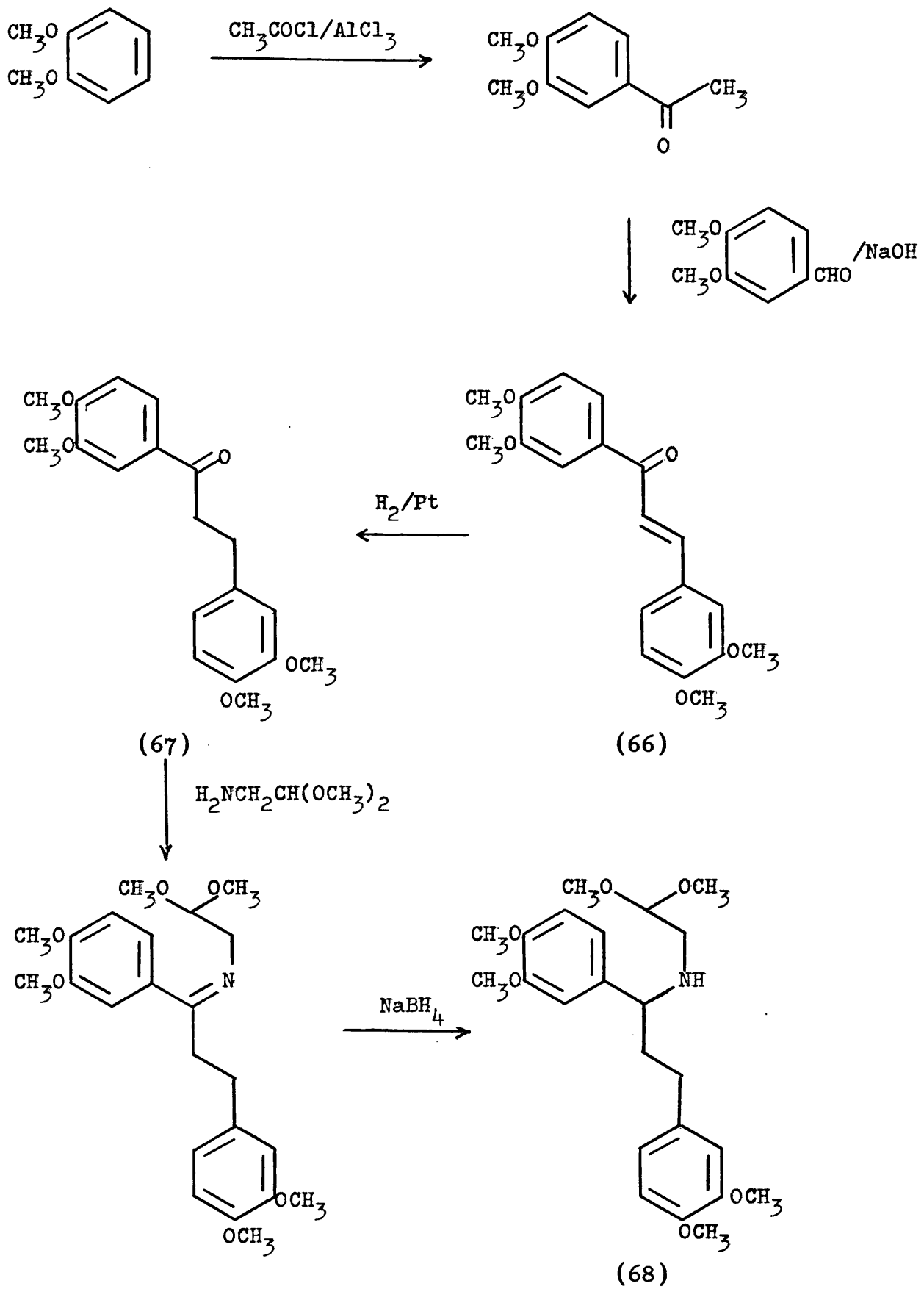
Scheme 7

The target compound chosen for this synthetic study was the tetramethoxyhomoisopavinane (64, $R_1=R_2=R_3=R_4=CH_3$, $R_5=H$), primarily because of the ease with which the required starting aminoacetal could be prepared, but also because after N-methylation comparison with Stermitz's compound (62) would be possible.

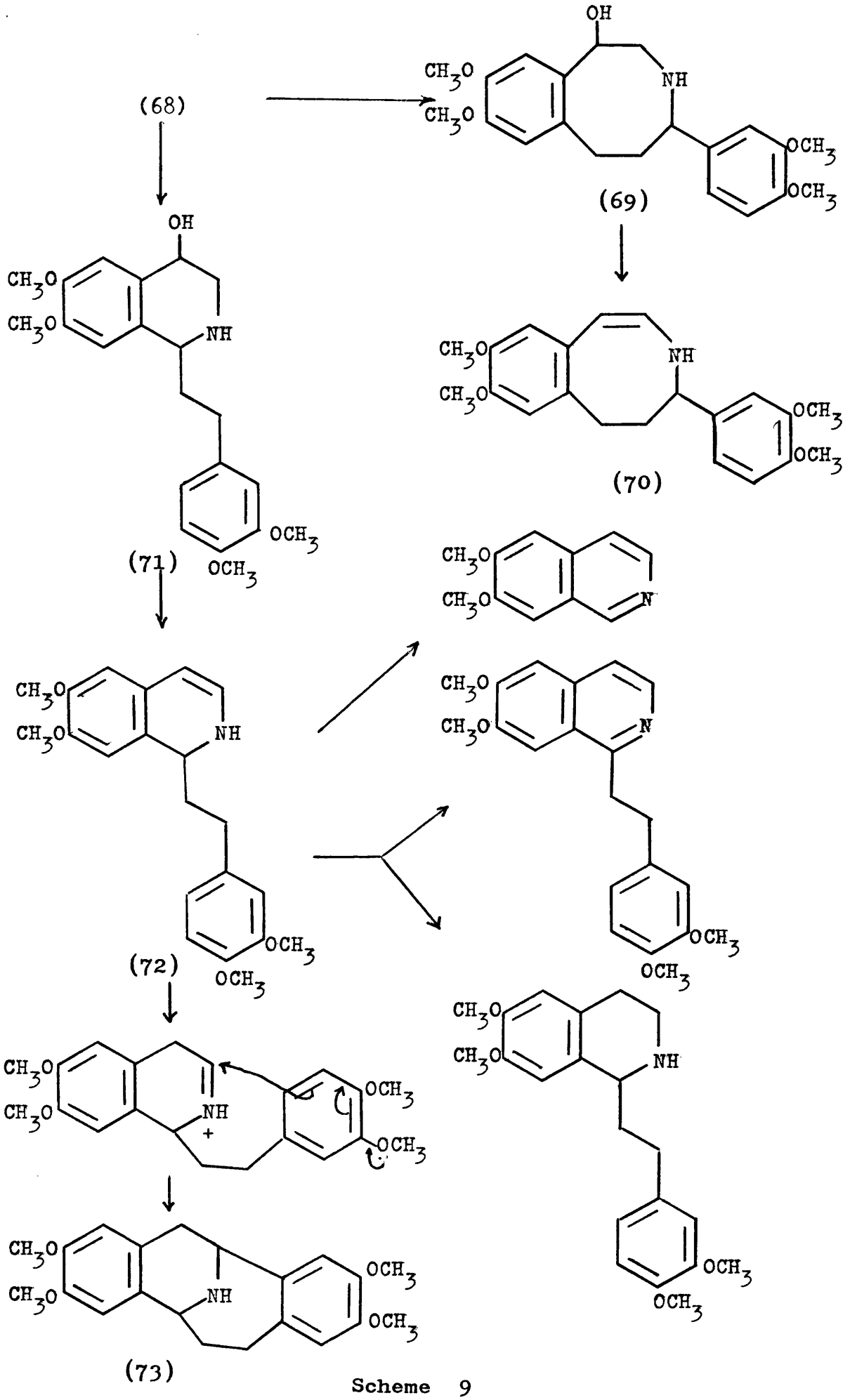
The required acetal (68) was prepared by the route outlined in scheme 8. Acylation of veratrole with acetyl chloride in the presence of aluminium chloride afforded, after distillation of the crude product, 3,4-dimethoxyacetophenone (65) as a colourless oil which crystallised upon standing. Aldol condensation with 3,4-dimethoxybenzaldehyde gave the chalcone (66) which, upon atmospheric hydrogenation in acetic acid over Adams catalyst at room temperature afforded the dihydrochalcone (67)[51]. Finally, condensation with aminoacetaldehyde dimethylacetal and reduction of the resultant imine with sodium borohydride gave the required acetal (68) as a colourless oil.

Treatment of the acetal (68) with ethanolic HCl afforded upon working up for bases a brown oil. Thin layer chromatography on silica using chloroform-methanol elution indicated the absence of starting material and a complex mixture consisting of two major products and at least four other components.

The cyclisation reaction was repeated using different acid concentrations, temperatures and reaction times, but in each case the same mixture of products was obtained. Possible side reactions are outlined in scheme 9. The alternative cyclisation to (69) followed by dehydration might afford the enamine (70), which could then undergo dimerisation. Dehydration of the intermediate 4-hydroxy-tetrahydroisoquinoline (71) would give the 1,2-dihydro-isoquinoline (72). This product could then undergo the typical reactions of 1,2-dihydroisoquinolines such as loss


CH3O
CH3O
CH3COCl/AlCl3
CH3
O
/NaOH
CHO
H2/Pt
OCH3
(67)
(66)
H2NCH2CH(OCH3)2
N
NaBH4
NH
(68)

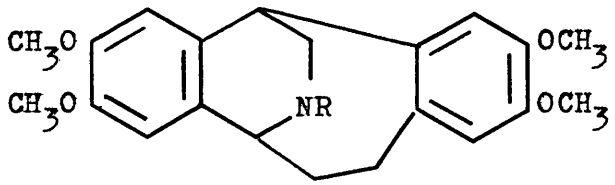
Scheme 8



Scheme 9

of the C_1 substituent, disproportionation, dimerisation or in this case, undergo protonation followed by cyclisation to the homopavinane (73).

Repeated attempts to separate the mixture of products by column chromatography using a number of solvent systems, resulted in only partial separation. Eventually careful column chromatography on silica with pure chloroform elution, followed by preparative layer chromatography on silica with multiple chloroform-methanol elution afforded the required homoisopavinane (74,R=H) as a beige amorphous solid in 39% yield. The product was identified by its nmr spectrum, which showed only four aromatic protons resonating as singlets and in particular, by its mass spectral fragmentation pattern (scheme 10). As in the case of the isopavinanes the molecular ion and (M-1) peak were strong, the molecular ion being the base peak of the spectrum in this case. Like the mass spectra of isopavinanes, the mass spectrum of this homoisopavinane showed a peak due to the fragment "a" arising by a retroDiels-Alder loss of the nitrogen bridge. However, unlike the isopavinanes, further fragmentation by loss of ethylene occurred to give a fairly strong peak due to the stable anthracene species "b". A strong peak due to the isoquinolyl ion "c" was observed as expected and all the proposed fragmentations were supported by the presence of the appropriate metastable ions.



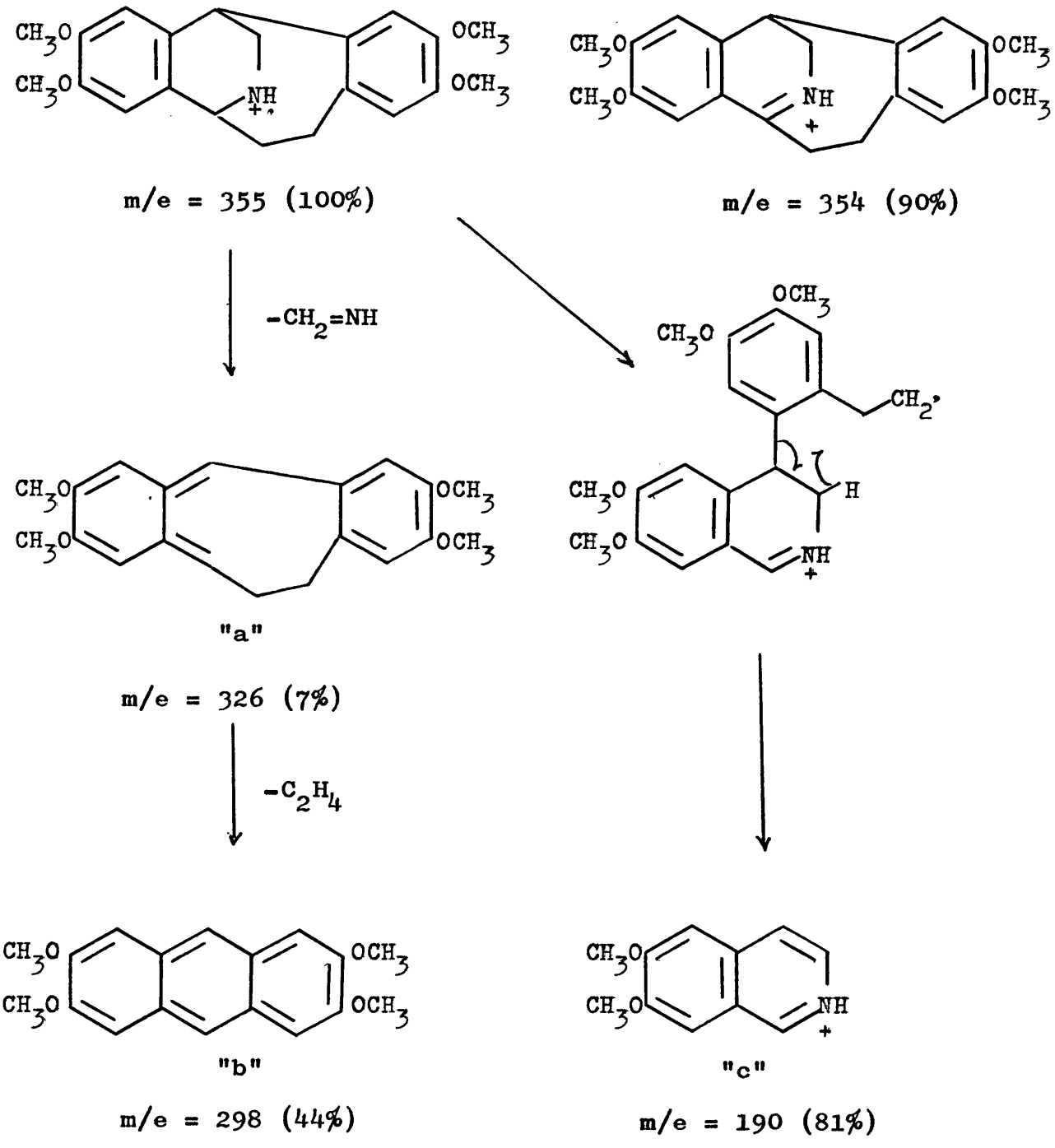
(74)

Despite numerous attempts from a number of solvents, the product could not be persuaded to crystallise. Although an analytically pure sample could not be obtained the analysis figures were in reasonably good agreement with prediction.

Treatment of a dilute acetone solution of the product with c. HCl afforded a crystalline hydrochloride. Once again although the hydrochloride was not analytically pure, the analysis was in reasonable agreement with prediction.

Treatment of the free base with formaldehyde, followed by sodium borohydride reduction afforded the N-methyl compound (74,R=CH_3). The nmr spectrum of this product again showed four aromatic protons resonating as singlets and, in addition to four methoxyl groups, a three proton singlet at 2.45 ppm due to the N-methyl group. That this product was the homoisopavinane and not the homopavinane (62) was confirmed by the mass spectrum which once again showed peaks due to the ions "a" and "b" (scheme 10) arising by retro Diels-Alder fragmentation followed by loss of ethylene. High resolution mass confirmed the formulae $C_{22}H_{27}NO_4$ and

$C_{18}H_{18}O_4$ for the molecular ion and the fragment ion "b" respectively.

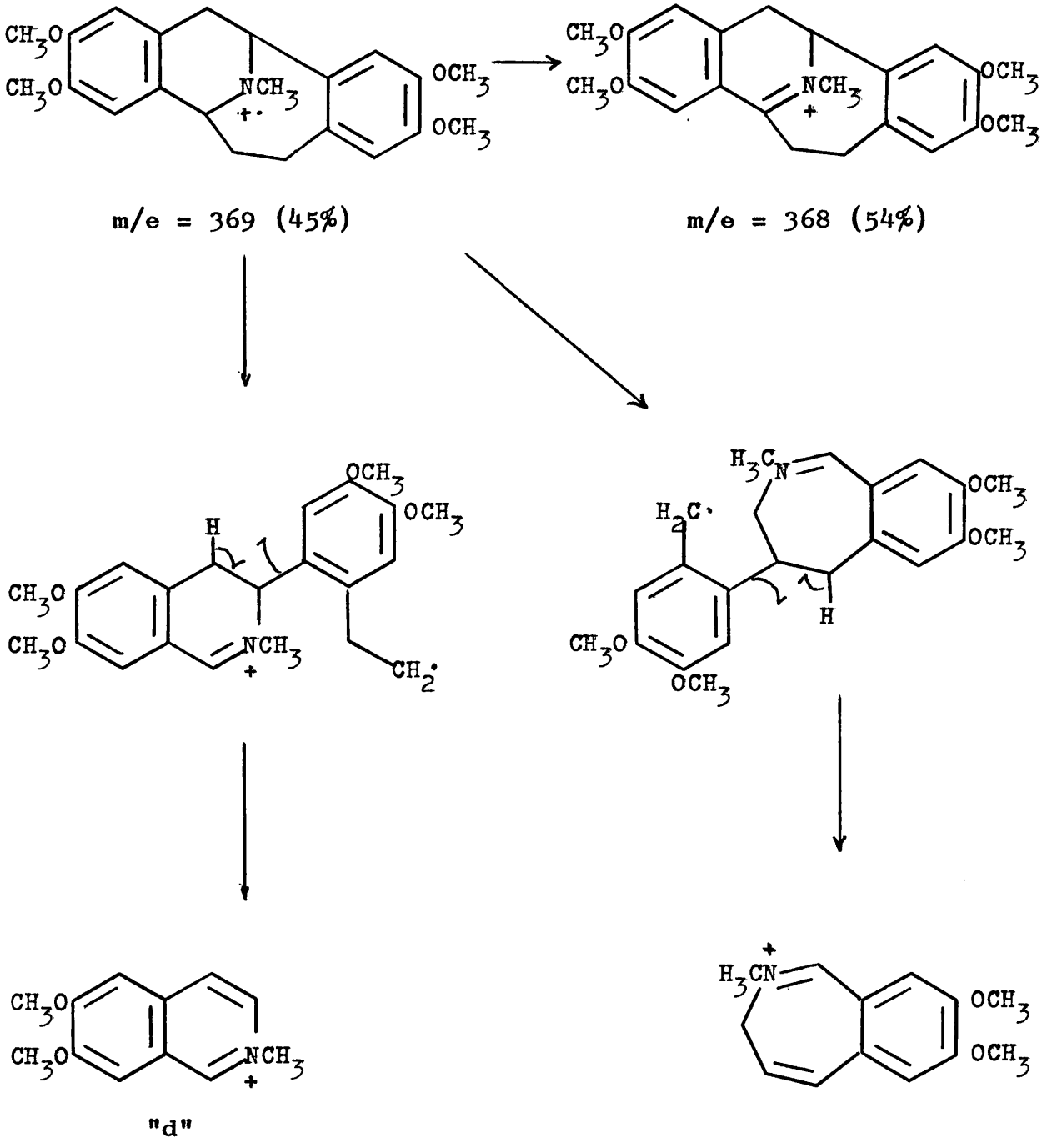


Scheme 10

The mass spectral data reported by Stermitz for the homopavinane (±)-homoargemonine (62) can be rationalised in terms of fragmentations similar to those observed for pavinanes (scheme 11). As in the case of the pavinanes, retro Diels-Alder loss of the nitrogen bridge is not possible because the structure is branched at both carbons α to the nitrogen. However, unlike the pavinanes, only one mode of fragmentation can give rise to an isoquinolyl ion of the type "d".

The other major component (11%) isolated from the cyclisation of (68) was a white solid melting at 106° and exhibiting the same UV spectrum as the homoisopavinane (74). The nmr spectrum of this product was more complex, showing complex absorption in the aromatic region, a broad deuterable signal at 4.2 ppm and six singlets in the methoxyl region of the spectrum. The mass spectrum exhibited small peaks at m/e 355 and 354. The base peak was located at m/e 341 and peaks at m/e 340 and 190 were almost as strong. Other strong peaks occurred at m/e 284 and 176 and metastable ions were observed at m/e 311, 285.5, 283, 106 and 91.

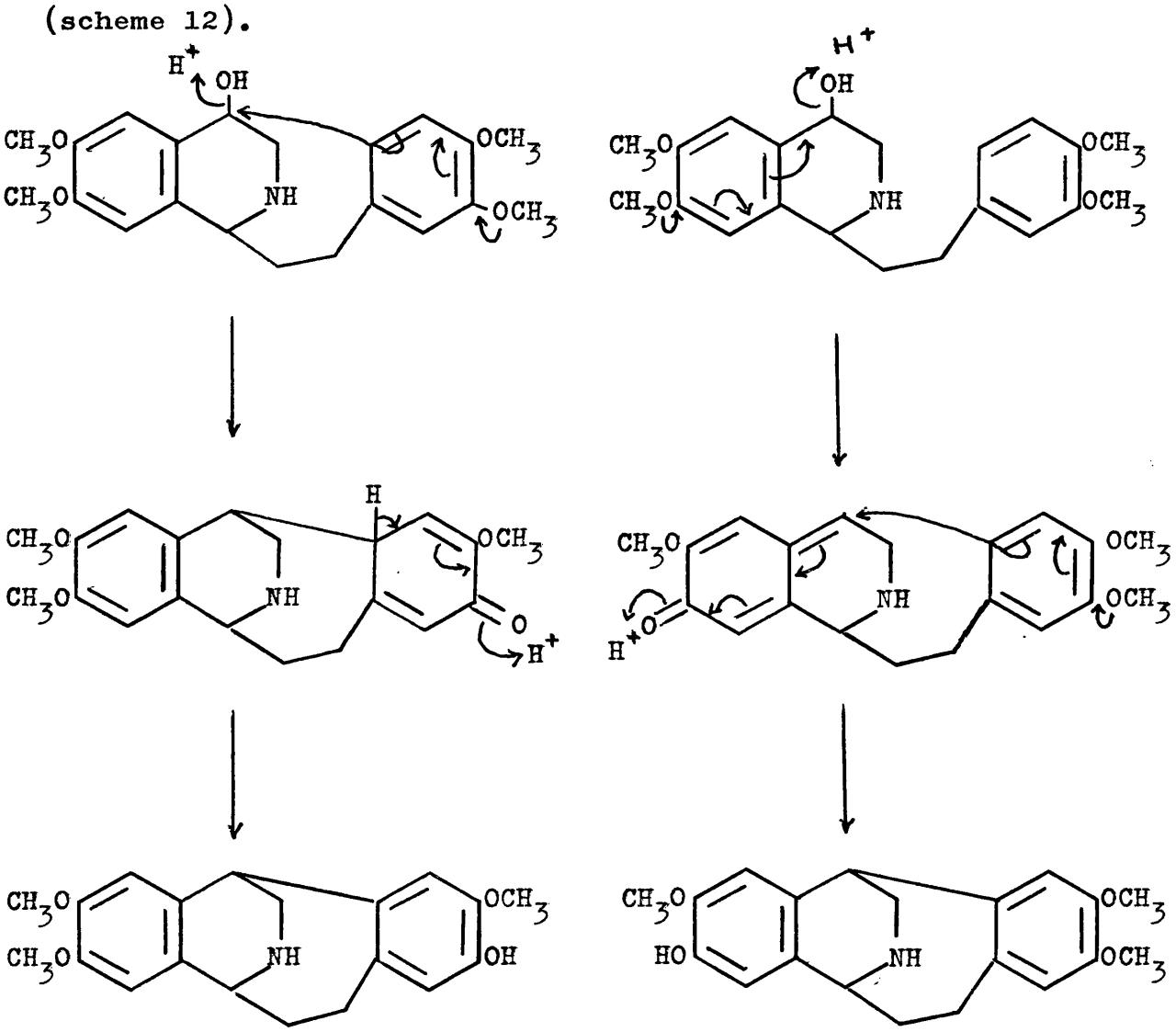
It was difficult to assign a structure on the basis of this evidence. The complexity of the methoxyl region of the nmr spectrum indicated that the fraction under examination was a mixture, although under a variety of thin layer chromatography conditions only one spot was observed. The fact that the methoxyl region of the nmr spectrum integrated to nine protons, the broad deuterable



Scheme 11

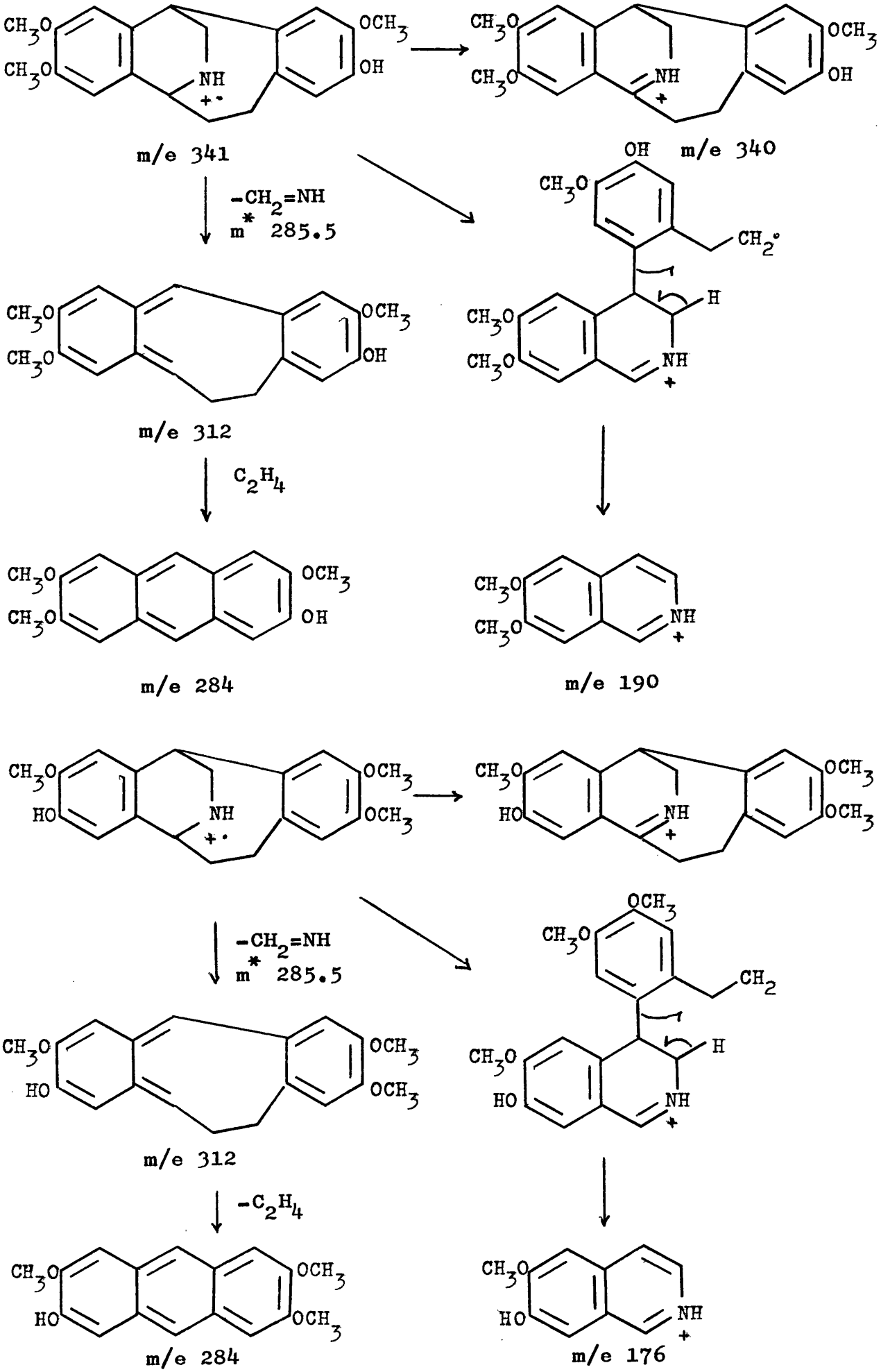
signal at 4.2 ppm and the mass spectral fragmentations, led the author to conclude that the fraction consisted of a mixture of two monodemethylated homoisopavinanes with the phenolic hydroxyl being located in opposite aromatic rings. The most probable structures for these monophenolic

homoisopavinanes are (75) and (76), as demethylation is most likely to occur <u>para</u> to the points of ring closure (scheme 12).



Scheme 12

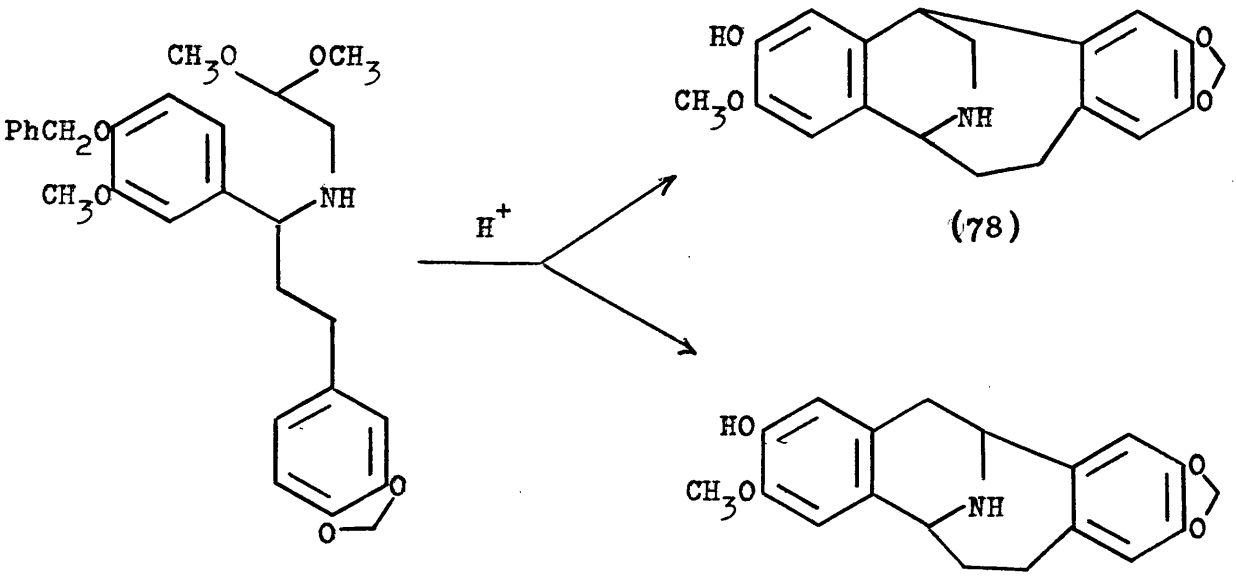
With the exception of the two small peaks at m/e 355 and 354, the mass spectrum of the fraction can readily be explained in terms of these two structures. Both (75) and (76) would give strong M^+ and $(M-1)^+$ ions at m/e 341 and 340.


m/e 341
m/e 340
-CH2=NH
m* 285.5
m/e 312
C2H4
m/e 284
m/e 190
m/e 312
-CH2=NH
m* 285.5
-C2H4
m/e 284
m/e 176

Scheme 13

They would both give retro Diels-Alder fragments at m/e 312 which, would both lose ethylene to give anthracene ions at m/e 284. Compound (75) would give a strong isoquinolyl ion at m/e 190 whereas compound (76) would give a corresponding fragment at m/e 176 scheme 13. The weak ions at m/e 355 and 354 may have been due to umpurity, although none was detected by thin layer chromatography. Alternatively, these latter ions may have been due to methyl transfer as has been found to occur with the isopavinanes[52,53] (see page 96). Support for the presence of phenolic hydroxyl was provided by the UV spectrum which showed a bathochromic shift upon addition of base.

As the next logical extension to this work it was decided to examine the cyclisation of the aminoacetal (77). It was thought that by analogy with the cyclisation of the similarly substituted homologous acetal (see chapter 1), cyclisation of this acetal might afford both the homo-isopavinane (78) and the homopavinane (79).



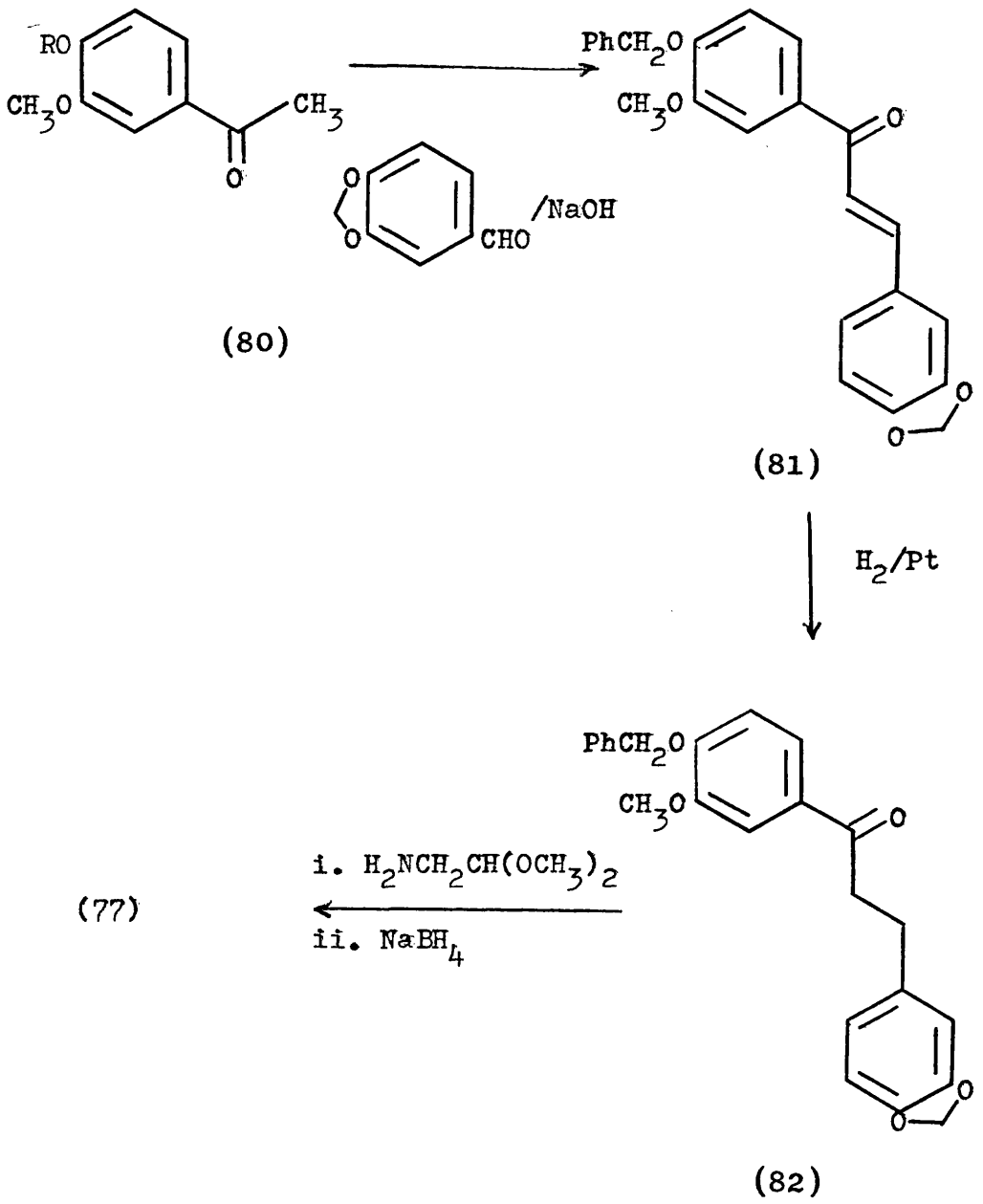
(77)

(78)

(79)

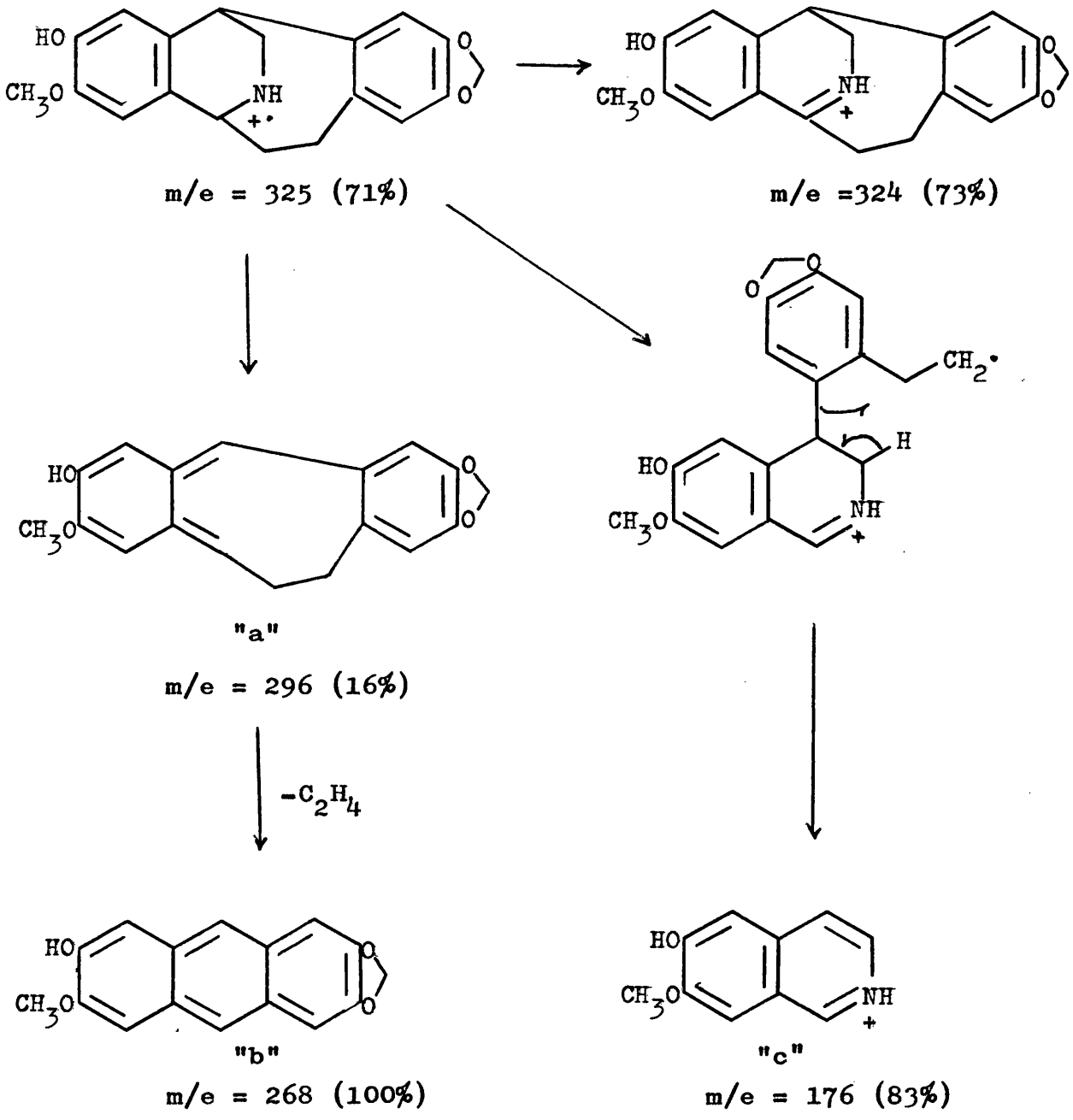
The acetal (77) was prepared by an analogous route to that used in the preparation of the tetramethoxy compound (68) scheme 14. Attempts to condense acetovanillone (78,R=H) with piperonal under basic conditions failed presumably due to the presence of the free hydroxyl group. Therefore the phenolic group was protected as the benzyl ether. Benzylation with benzyl chloride in the presence of sodium hydroxide resulted in a mixture of products. However, the pure O-benzyl acetovanillone (80,R=$PhCH_2$-) could be obtained by dissolving the crude product in chloroform, filtering off insoluble products, washing the solution with water, evaporating the solvent and re-crystallising the product from ethanol. Condensation with piperonal afforded the chalcone (81). Difficulty was encountered in finding a suitable solvent in which to carry out the hydrogenation of (81), as it was only sparingly soluble in the common hydrogenation solvents. Attempts to hydrogenate a suspension of (81) in acetic acid resulted after 72 hours in little uptake of hydrogen. Eventually hydrogenation of a very dilute acetic acid solution of (81) afforded the required dihydrochalcone (82) in reasonably good yield. Condensation with aminoacetaldehydedimethylacetal and reduction of the resultant imine with sodium borohydride then afforded the required acetal as a colourless oil in excellent yield.

Treatment of (77) with ethanolic HCl resulted in a mixture of bases consisting of one major component and at least four others. Column chromatography on silica



Scheme 14

using chloroform-methanol elution afforded the homo-isopavinane (78) as a beige solid in approximately 63% yield. The product was again identified by its nmr spectrum which showed only four aromatic protons, resonating as singlets and in particular by its mass spectral fragmentation pattern summarized in scheme 15.

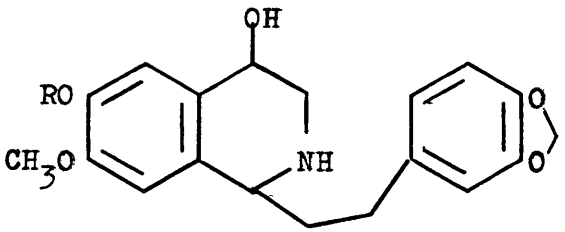


Scheme 15

Once again the M^+ and $(M-1)^+$ peaks were strong and the ion "a" corresponding to retro Diels Alder fragmentation was observed. The base peak was provided by the anthracene species "b" arising by loss of ethylene from the ion "a".

The expected peak due to the isoquinolyl ion "c" was strong. In this case strong peaks were also observed at $(M+14)^+$ and $(M+13)^+$, presumably arising by methyl transfer[51-53]. A strong peak at m/e 190 was attributed to an isoquinolyl fragment formed from the (M+14) ion.

The homopavinane (79) was not isolated or detected in the reaction mixture. The absence of this product is probably due to the fact that cyclisation of the intermediate 1-phenethyl-4-hydroxyisoquinoline (83) to the homoisopavinane occurs too rapidly to allow time for the necessary dehydration, protonation and cyclisation to the homopavinane system. This might be expected since the greater flexibility of the 1-phenethyl group compared with the 1-benzyl group would mean that the steric requirement in the transition state leading to homoisopavinanes would be lower than that in the transition state leading to isopavinanes.



(81)

EXPERIMENTAL

3,4-dimethoxyacetophenone (65)

Veratrole (100g) was dissolved in CH_2Cl_2 ($400cm^3$) and $AlCl_3$ (100g) added portionwise with stirring. When all the $AlCl_3$ had dissolved the mixture was cooled in an ice bath and acetyl chloride (56g) added dropwise. The wine red mixture was stirred at room temperature for 2 hours and then poured into ice water ($400cm^3$). The organic layer was separated and the aqueous layer extracted with further CH_2Cl_2 ($100cm^3$). The combined organic extracts were washed with 2M NaOH ($100cm^3$), H_2O ($100cm^3$), dried (Na_2SO_4), and evaporated to yield a yellow oil which was distilled under reduced pressure. A fraction collected between 68 and 70° at 2 mm pressure was shown by G.C. (OV1/150°) to consist mainly of unchanged veratrole. The required product collected at 140-142° at 2 mm and was shown by G.C. to contain less than 2% unchanged veratrole. The product crystallised as white prisms (100.5g 77%) on standing. mp 42-44°, λ max 211, 230, 274, 304. ν max 1664, nmr ($CDCl_3$) 7.55 d.d [1] J ortho = 8Hz, J meta = 2Hz. (Ar-H_6), 7.5 broad s [1] (ar-Hz), 6.88 d [1] J ortho = 8Hz. (Ar-H_5), 3.94 two s [6] (2xOCH_3), 2.56 s [3] (-$COCH_3$).

1,3-bis(3,4-dimethoxyphenyl)propenone (66)

3,4-dimethoxyacetophenone (100g) and 3,4-dimethoxyacetaldehyde (92.25g) were dissolved in 95% EtOH ($800cm^3$) and 2M NaOH ($100cm^3$) added. The resultant solution was left to stand for 24 hours with occassional shaking. Upon chilling, the required chalcone cyrstallised as yellow needles

(83%) mp 102-103°. λ max 212, 244, 357 ν max 1647cm^{-1} (C=O) nmr ($CDCl_3$) 7.9-6.8 complex [8] (6xAr-H+-CH=CH-), 3.98 three s [12] (4xOCH_3).

1,3-bis(3,4-dimethoxyphenyl)propan-1-one (67)

The chalcone (66) (10g) was dissolved in glacial acetic acid (60cm^3) and hydrogenated at atmospheric pressure over Adams catalyst (0.1g) at room temperature. When the uptake of hydrogen was complete the solution was filtered and diluted with water, whereupon the product crystallised as white needles (64%) mp 90-91° ex Et_2O λ max 213, 231, 276, 303 ν max 1665cm^{-1} (C=O) nmr ($CDCl_3$) 7.55 d.d [1] J ortho = 8Hz, J meta = 2Hz (Ar-H_6), 7.5 s [1] (Ar-H_2) 6.86 d [1] J ortho = 8Hz (Ar-H_5) 6.77 s [3] (3xAr-H), 3.94 two s [6] (2xOCH_3), 3.87 two s [6] (2xOCH_3), 3.4-2.9 complex [4] (CH_2-CH_2).

N-(1,3-bis(3,4-dimethoxyphenyl)propyl)aminoacetaldehyde dimethylacetal (68)

The above ketone (6g) and aminoacetaldehydedimethylacetal (30cm^3) were heated under reflux in an atmosphere of N_2 for 4 hours. The resultant solution was diluted with 95% EtOH (100cm^3) and $NaBH_4$ (1g) added portionwise with stirring. The mixture was stirred overnight at room temperature and then the ethanol and excess aminoacetaldehyde-dimethylacetal were distilled off under reduced pressure. The residue was dissolved in Et_2O (100cm^3) and the resultant solution washed with H_2O (2x50cm^3) and extracted with ice cold 2M H_2SO_4 (3x50cm^3). The ether residues afforded on evaporation a neutral compound shown to be 1,3-bis(3,4-dimethoxyphenyl) propan-1-ol ν max 3500 nmr ($CDCl_3$) 7.0-6.6 complex [6]

(6xAr-H), 4.62 t J = 6Hz [1] ($\succ$CH-OH), 3.86 two s [12] ($4xOCH_3$), 2.8-2.5 complex [2] and 2.2-1.8 complex [2] ($-CH_2-CH_2-$), 2.0 broad [1] removed by D_2O (OH).

The acid extracts were washed with Et_2O ($50cm^3$), basified with 2M NH_3 and extracted with Et_2O ($3x100cm^3$). Evaporation of the dried (Na_2SO_4) extracts afforded the required acetal as a colourless oil (61%) λ max (ε) 235 (17,200), 282 (7,800) nmr ($CDCl_3$) 7.0-6.58 complex [6] (6xAr-H), 4.4 t, J = 5Hz [1] ($\underline{CH}(OCH_3)_2$), 3.9 s and 3.85 s [12] ($4xOCH_3$), 3.52 t J = 7Hz [1] collapsed to singlet by irradiation at 1.96 ppm ($\succ$CH-N) 3.35 s [3] and 3.30 s [3] ($CH(O\underline{CH}_3)_2$), 2.54 d J = 5Hz [2] collapsed to singlet by irradiation at 4.4 ppm ($-CH_2-N$) 2.5 t J = 8Hz [2] ($Ar-CH_2$), 2.0 m [2] ($-CH_2-\underline{CH}_2-CH\prec$), 1.67 broad s [1] removed by D_2O (NH).

Acid cyclisation of (68)

The above acetal (1g) was dissolved in EtOH ($50cm^3$) and conc HCl ($50cm^3$) added. The mixture was refluxed on a steambath for 4 hours, poured into water ($200cm^3$), washed with Et_2O ($2x50cm^3$) basified with conc ammonia and extracted with Et_2O ($3x100cm^3$). Evaporation of the dried (Na_2SO_4) extracts afforded a brown oil (0.76g). TLC (SiO_2/10%CH_3OH-$CHCl_3$) showed two major components Rf 0.40 and 0.20 and at least four other components with Rf 0.75, 0.69, 0.58 and 0.1. Column chromatography ($SiO_2/CHCl_3$) afforded partially separated samples of the two major components. These were further purified by preparative layer chromatography on 1 mm silica PF_{254} layers using multiple elution with 5% CH_3OH in $CHCl_3$. The samples obtained by soxhlet

extraction of the silica bands were dissolved in 2M HCl, washed with Et_2O, basified with NH_3 and extracted into Et_2O.

Evaporation of one of the ether extracts (Rf 0.40) afforded the homoisopavinane (74,R=H) (39%) as a white amorphous solid. λ max (ε) 233 (13,500), 287 (6,600) nmr ($CDCl_3$) 6.75 s [2] (2xAr-H), 6.57 s [1] (Ar-H), 6.51 s [1] (Ar-H), 4.46 broad s [1] (CH-N), 4.02 broad s [1] (Ar-CH-Ar), 3.86-3.79 four singlets [12] ($4xOCH_3$), 2.88 broad s [2] ($-C\underline{H}_2-NH$), 2.26 broad s [1]removed by D_2O (NH), 2.0 broad [4] (CH_2-CH_2) mass m/e 355 $(M)^+$ [100%], 354 $(M-1)^+$ [90%], 326 [7%], 298 [44%], 190 [81%] M^*=272.4 (Found: C, 69.1, H 7.3, N 3.6, $C_{21}H_{25}NO_4$ requires C 71.0, H 7.0, N 3.9%). hydrochloride: Beige needles mp 242-244° (Found: C 63.2, H 6.7, N 3.7, Cl 9.3, $C_{21}C_{26}NO_4Cl$ requires C 64.4, H 6.6, N 3.6, Cl 9.0%).

Evaporation of the other ether extract afforded a white solid (11%) mp 106° λ max (ε) 232 (10,800), 287 (6,200). On addition of base λ max 232, 293 and 300 sh. nmr ($CDCl_3$) 6.88-6.4m, 4.49 broad, 4.2 broad removed by D_2O, 4.0 broad, 3.92-3.74 six singlets, 2.88 broad, 2.0 broad mass m/e 355 [8%], 354 [9%], 342 [23%], 341 [100%], 340 [96%], 312 [9%], 284 [61%], 190 [97%], 176 [52%], M^* 311, 285.5, 283, 106, 91. (Found: C 68.6, H 6.8, N 3.9, $C_{20}H_{23}NO_4$ requires C 70.4, H 6.7, N 4.1%).

N-methylation of the homoisopavinane (72,R=H)

The homoisopavinane (74R=H) (113mg) was dissolved in MeOH ($10cm^3$) and formaldehyde 37-41% w/v ($1cm^3$) added. After stirring for 1 hour, $NaBH_4$ (0.2g) was added portionwise

and the mixture stirred overnight. The solution was acidified with dil HCl and evaporated. The residue was dissolved in H_2O ($25cm^3$) and the solution made basic with dilute NH_3. The mixture was extracted with CH_2Cl_2 ($2x25cm^3$) and the extracts washed with H_2O ($12.5cm^3$). Evaporation of the dried (Na_2SO_4) extracts afforded the N-methylhomoisopavinane (74,R=CH_3) as a white amorphous solid (85%) λ max 233 (12,400), 285 (6,700) nmr ($CDCl_3$) 6.77 s [2] (2xAr-H), 6.55 s [1] (Ar-H), 6.50 s [1] (Ar-H), 4.0 t [1] ($\geq$C<u>H</u>-NCH_3), 3.92-3.76 three s [13] (4xOCH_3+Ar-CH-Ar), 3.04 d.d J_1= 10Hz, J_2=2Hz, [1] and 2.60 d.d J_1=10Hz, J_2=4Hz [1] ($\geq$CH-<u>CH_2</u>-N) 2.45 s [3] (N-CH_3) 2.3-1.6 complex [4] (-CH_2-CH_2-) mass m/e 369 $(M)^+$ [93%], 368 $(M-1)^+$ [97%], 338 [4%], 326 [4%], 311 [4%], 298 [19%], 218 [3%], 204 [100%]. High resolution mass gave 369.1926 and 298.1220, $C_{22}H_{27}NO_4$ and $C_{18}H_{18}O_4$ require 369.1940 and 298.1205 respectively.

hydrochloride: Colourless needles mp 220-223° ex CH_3COCH_3. (Found: C 62.3, H 6.9, N 3.3, Cl 8.5, $C_{22}H_{28}NO_4Cl$. C 65.1, H 6.9, N 3.5, Cl 8.8%).

3-methoxy-4-benzyloxyacetophenone (80,R=$PhCH_2$)

Sodium hydroxide (12g) in H_2O ($30cm^3$) was added to a solution of acetovanillone (33.2g) in 95% EtOH ($60cm^3$). The mixture was refluxed for 30 minutes and benzylchloride (25.3g) added dropwise. After refluxing for a further 5 hours the mixture was chilled to 5° overnight, whereupon the required product crystallised as yellow prisms. The crude product was dissolved in CH_2Cl_2 ($200cm^3$) and the

resultant solution filtered, washed with H_2O (2x50cm^3) and evaporated. The residue was crystallised from ethanol to afford pure 3-methoxy-4-benzyloxy-acetophenone as beige needles (50%) mp 81-83°. λ max 233, 277, 306. nmr ($CDCl_3$) 7.6-7.2 complex [7] ($C_6\underline{H}_5$-CH_2+2xAr-H) 6.85 d J ortho = 9Hz [1] (Ar-H_5), 5.2 s [2] (C_6H_5-$C\underline{H}_2$-O), 3.9 s [3] (OCH_3), 2.5 s [3] (CH_3CO-).

1-(3-methoxy-4-benzyloxyphenyl)-3-(3,4-methylenedioxyphenyl) propenone (81)

3-methoxy-4-benzyloxy acetophenone (23.43g) and 3,4-methylenedioxybenzaldehyde (13.73g) were dissolved in 95% EtOH (130cm^3) and 2M NaOH (20cm^3) added whereupon the required product immediately crystallised. After chilling overnight the product was filtered off and recrystallised from EtOH. Yellow needles (78%) mp 137-138° λ max 218, 235 and 359. nmr ($CDCl_3$) 7.84-6.74 complex [13] (aromatics + -CH=CH-), 5.96 s [2] (CH_2O_2), 5.18 s [2] ($PhC\underline{H}_2O$), 3.92 s [3] (OCH_3).

1-(3-methoxy-4-benzyloxyphenyl)-3-(3,4-methylene dioxyphenyl)propan-1-one (82)

The above chalcone (5g) was dissolved in glacial acetic acid (150cm^3) and stirred under an atmosphere of H_2 in the presence of Adams catalyst (0.2g) for 3 days. The solution was filtered and then evaporated and the residue crystallised from EtOH to afford the required ketone as white needles (66%) mp 93.5-94°. λ max 235, 277. nmr ($CDCl_3$) 7.6-7.2 complex [7], 6.88 d J = 8Hz [1] and 6.71 s [3] (aromatics), 5.90 s [2] (CH_2O_2), 5.21 s [2] ($PhC\underline{H}_2O$),

3.93 s [3] (OCH_3) 3.32-2.84 complex [4] (CH_2-CH_2).

N-(1-(3-methoxy-4-benzyloxyphenyl)-3-(3,4-methylene dioxyphenyl)propyl)aminoacetaldehyde dimethylacetal (77)

The ketone (82) (3.0g) and aminoacetaldehyde dimethylacetal ($15cm^3$) were heated under reflux in an atmosphere of N_2 for 5 hours. The resultant solution was diluted with 95% EtOH ($50cm^3$) and $NaBH_4$ (0.5g) added portionwise with stirring. The mixture was stirred overnight at room temperature and then the ethanol and excess aminoacetaldehyde dimethylacetal distilled off under reduced pressure. The residue was dissolved in Et_2O ($100cm^3$) and the resultant solution washed with H_2O ($2x50cm^3$) and extracted with ice cold 2M H_2SO_4 ($3x50cm^3$). The acid solution was washed with Et_2O ($100cm^3$), basified with 2M NH_3 and extracted with Et_2O ($3x100cm^3$). Evaporation of the dried (Na_2SO_4) extracts afforded the required acetal as a colourless oil (61%) λ max (ε) 223 sh (13,800), 234 (15,800), 283 (8,300) nmr ($CDCl_3$) 7.5-7.18 complex [5] (Ph-CH_2-O), 6.9-6.4 complex [6] (6xAr-H), 5.83 s [2] (CH_2O_2) 5.06 s 2 (Ph-CH_2-O), 4.3 t J = 5Hz 1 (-$CH(OCH_3)_2$), 3.83 s [3] (OCH_3), 3.42 t J = 6Hz [1] collapsed to singlet by irradiation at 1.91 ($>$CH-N$<$), 3.28 s [3] and 3.23 s [3] ($CH(OCH_3)_2$), 2.48 d J = 5Hz [2] collapsed to singlet by irradiation at 4.3 (CH_2-N-), 2.4 t J = 8Hz [2] (Ar-CH_2) 1.91 m [2] (CH_2-CH_2-CH), 1.52 broad s [1] removed by D_2O (NH).

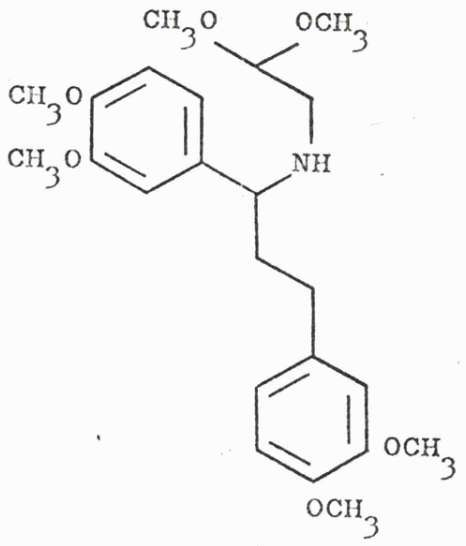
Acid cyclisation of (77)

The above acetal (1g) was dissolved in EtOH ($50cm^3$) and conc HCl ($50cm^3$) added. The mixture was refluxed on a

steam bath for 4 hours, poured into water ($200cm^3$) and the resultant solution washed with Et_2O ($2x50cm^3$). The pH was adjusted to 9 with dilute ammonia and the mixture extracted with CH_2Cl_2 ($3x100cm^3$). Evaporation of the dried (Na_2SO_4) extracts afforded a yellow gum. TLC (SiO_2/10%CH_3OH-$CHCl_3$) showed one major component Rf 0.17. Column chromatography (SiO_2/1%CH_3OH-$CHCl_3$) afforded the homoisopavinane (78) as a beige solid (63%) λ max (ε) 224 (7,500), 291 (5,300). On addition of NaOH λ max (ε) 224 (9,700), 245 (7,600), 297 (5,700). nmr ($CDCl_3$) 6.75 s [1] , 6.72 s [1] 6.55 s [1] , 6.50 s [1] (4xAr-H) 5.90 s [2] (CH_2O_2), 5.50 broad s [2] removed by D_2O (OH+NH), 4.52 broad s [1] ($\rangle$CH-N), 3.95 broad s [1] (Ar-<u>CH</u>-Ar), 3.80 s [3] (OCH_3), 2.90 broad s [2] (-<u>CH_2</u>-NH-) 2.02 broad [4] (-CH_2-CH_2-) mass m/e 339 $(M+14)^+$ [54%] 338 $(M+13)^+$ [64%] , 325 $(M)^+$ [71%] , 324 $(M+1)^+$ [73%] , 296 [16%] , 268 [100%] , 190 [89%] , 176 [83%] M^* 242.5.

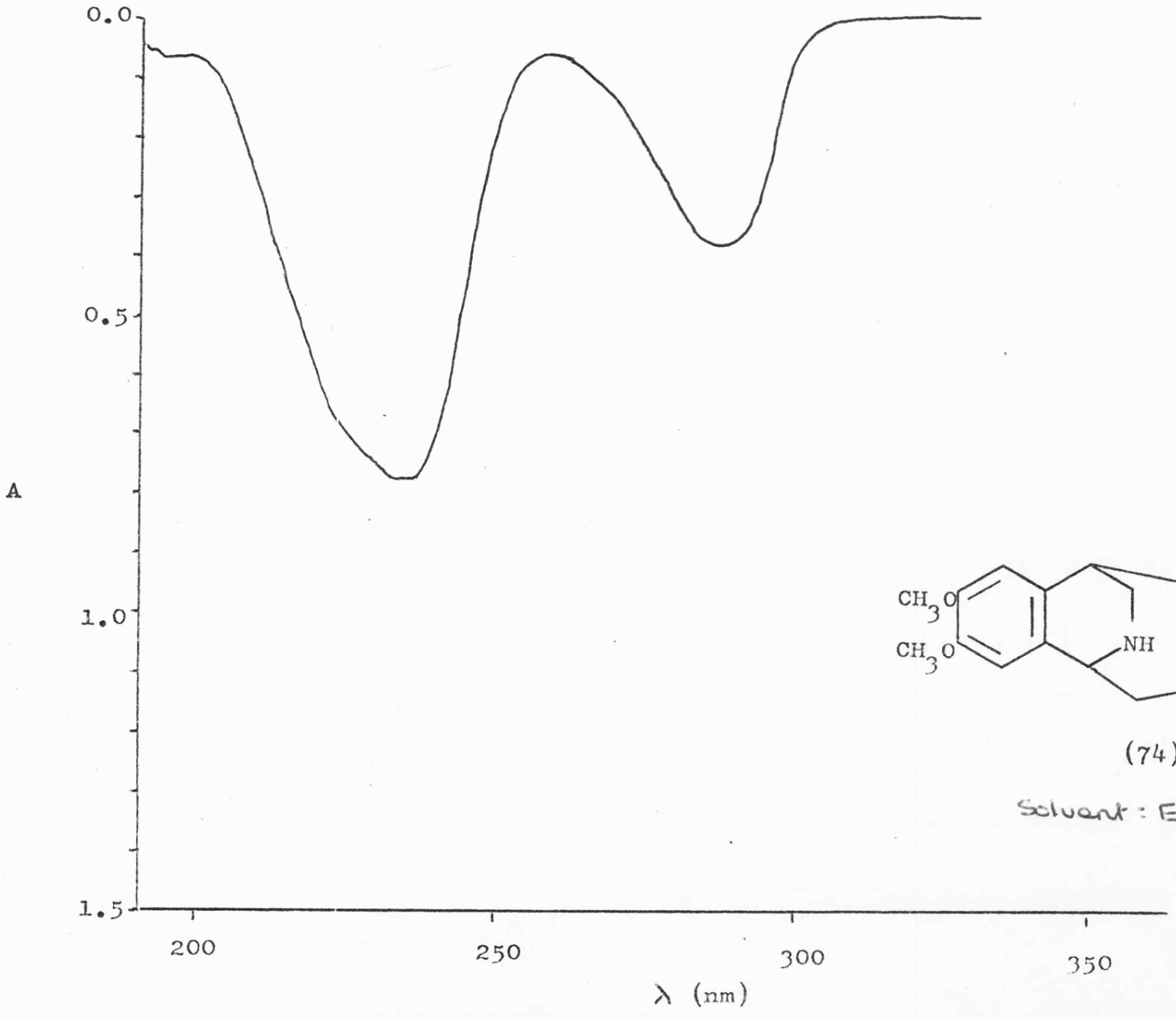
hydrochloride: Beige needles mp 230-232° d. (Found: C 63.4, H 5.7, N 3.7, Cl 9.4 $C_{19}H_{20}NO_4Cl$ requires C 63.1, H 5.5, N 3.9, Cl 9.8).

SPECTRA



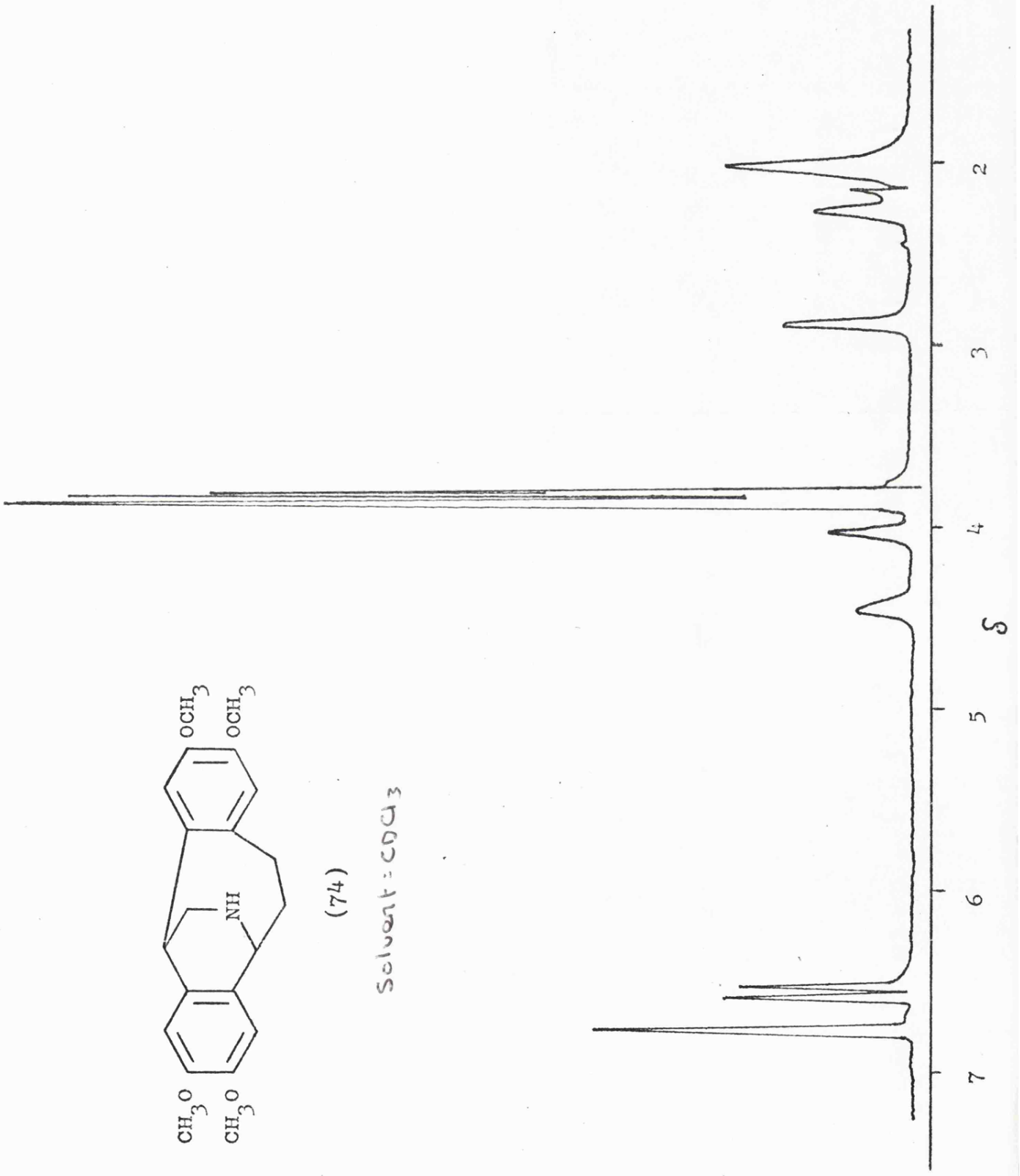
(68)

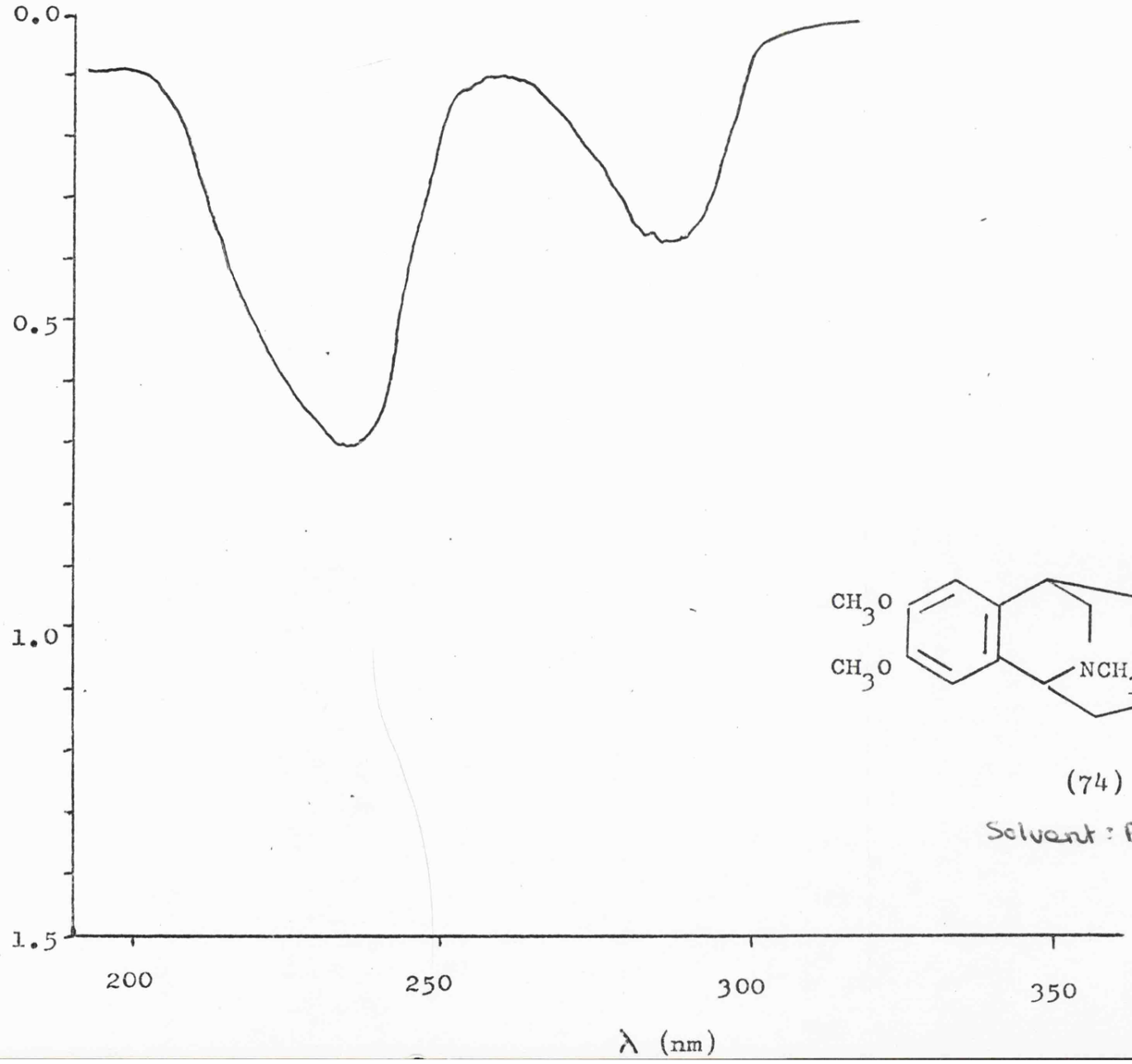
Solvent : $CDCl_3$



(74)

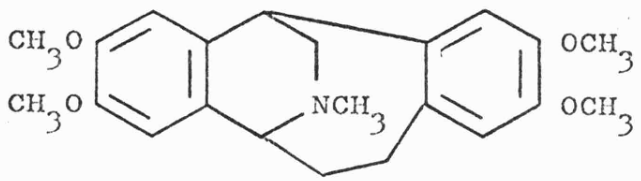
Solvent : EtOH.


OCH3
OCH3
NH
CH3O
CH3O
(74)
Solvent: CDCl3
7
6
5
4
3
2
δ



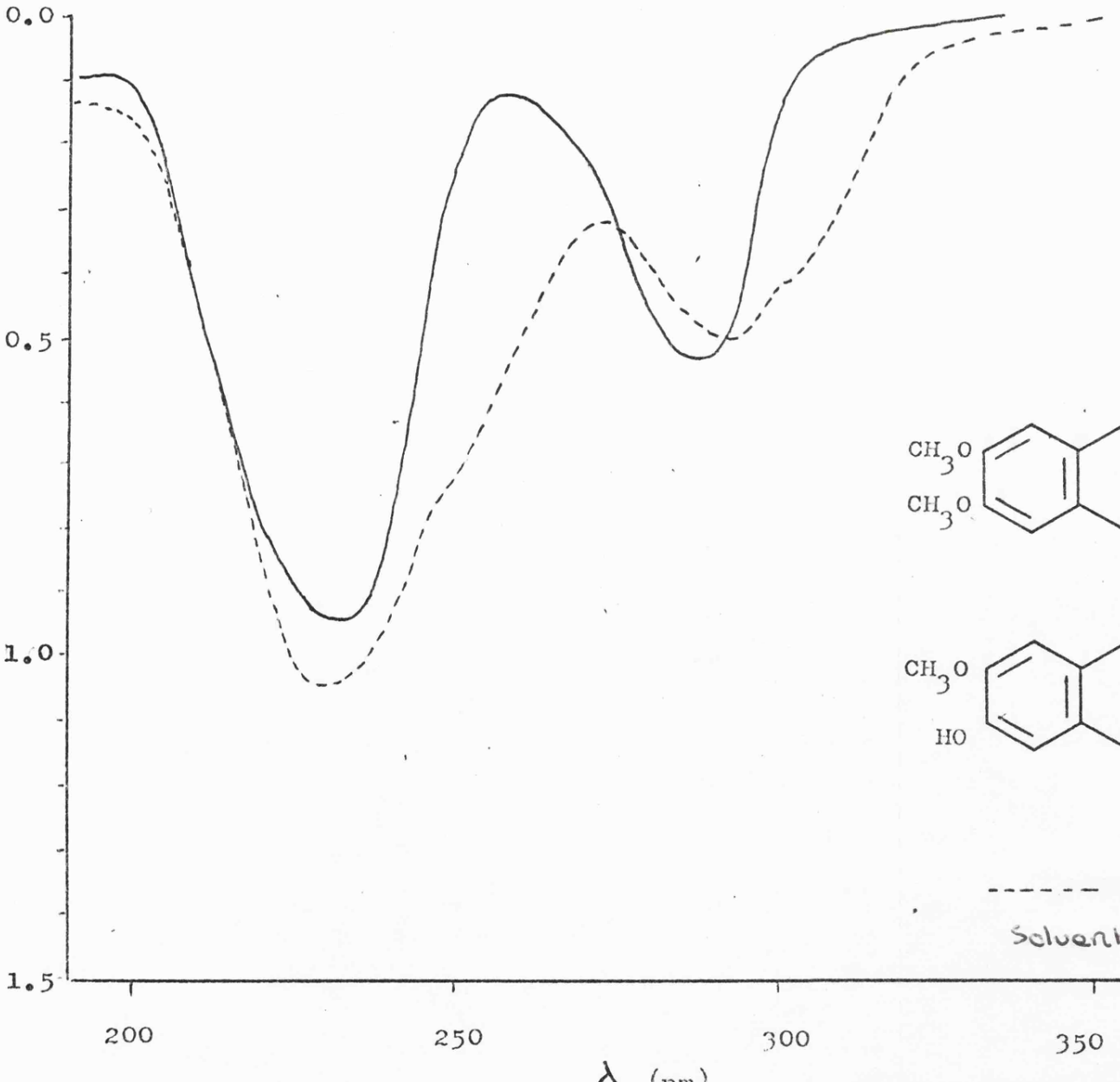
(74)

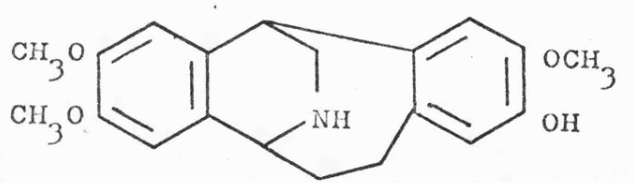
Solvent : EtOH



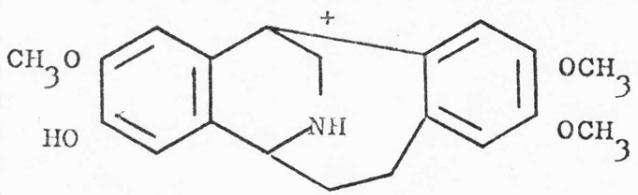
(74)

Solvent : $CDCl_3$





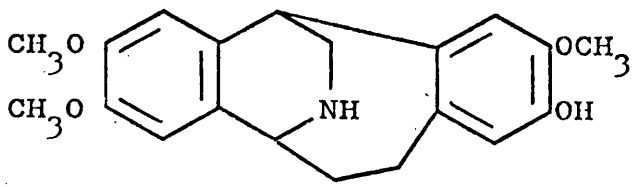
(75)



(76)

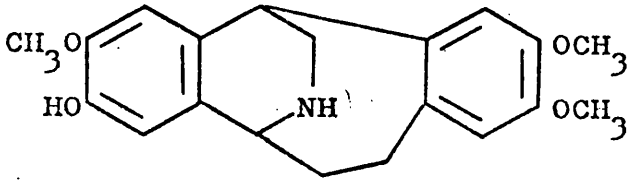
------ = + NaOH

Solvent : EtOH



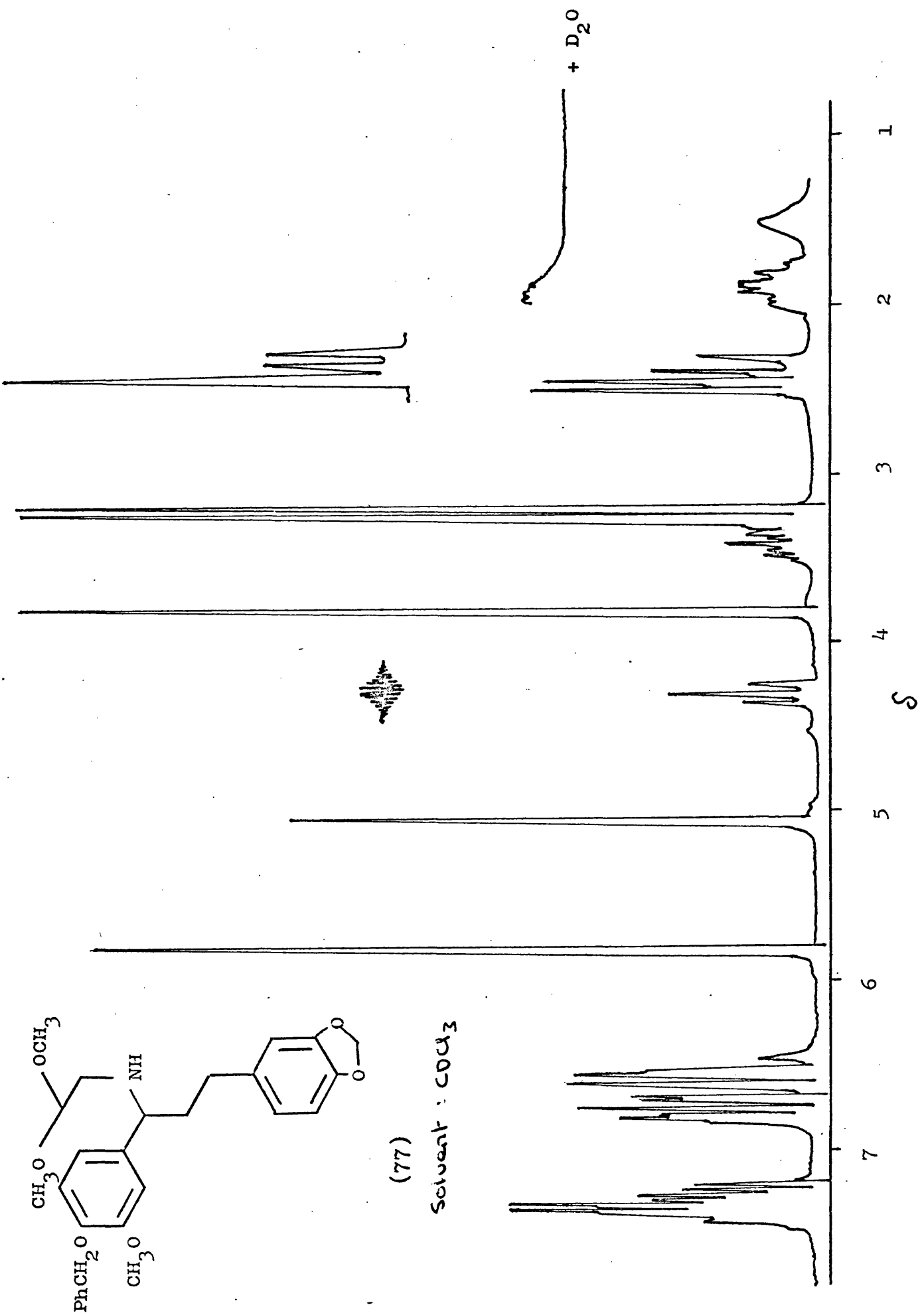
(75)

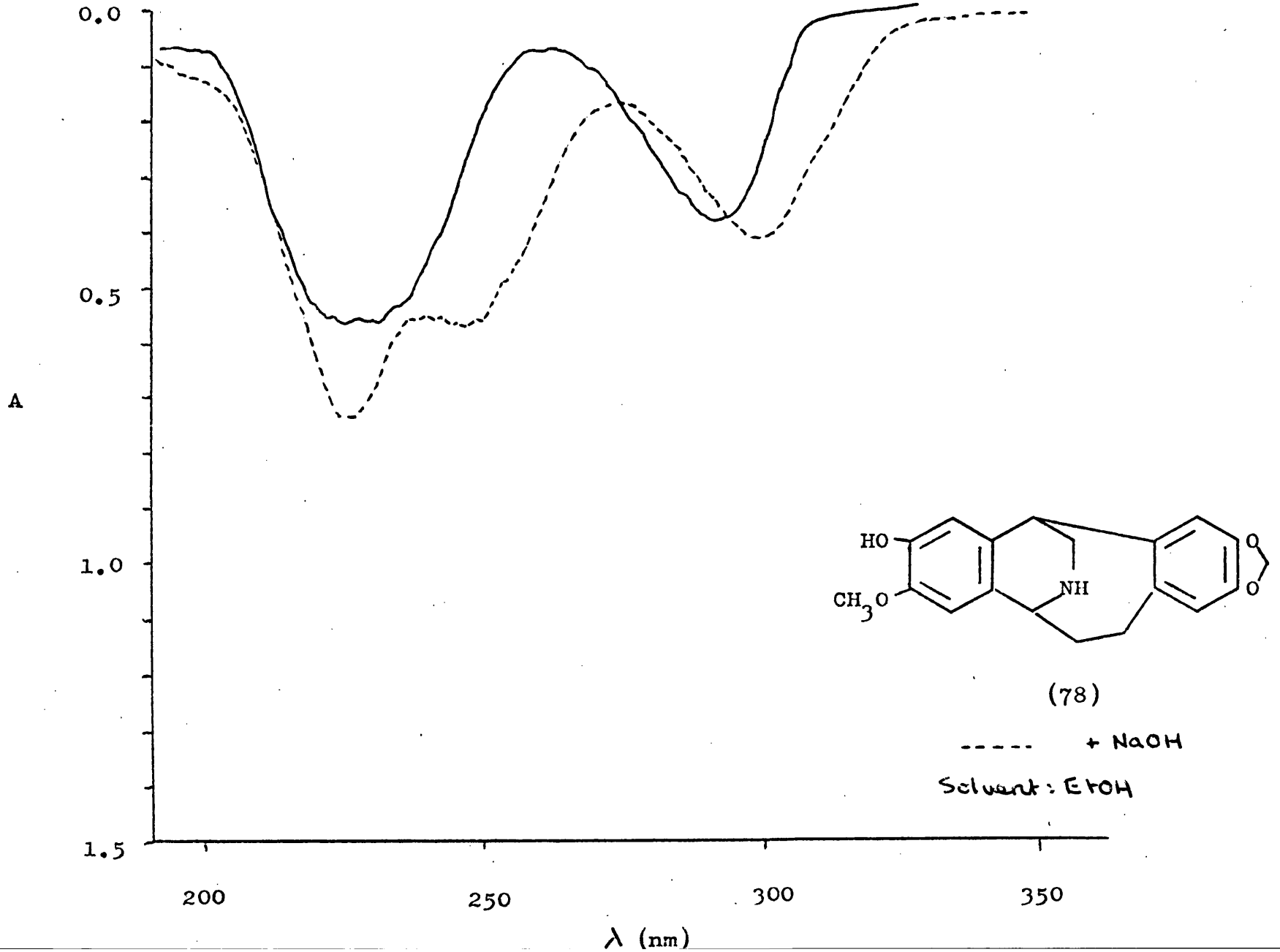
+

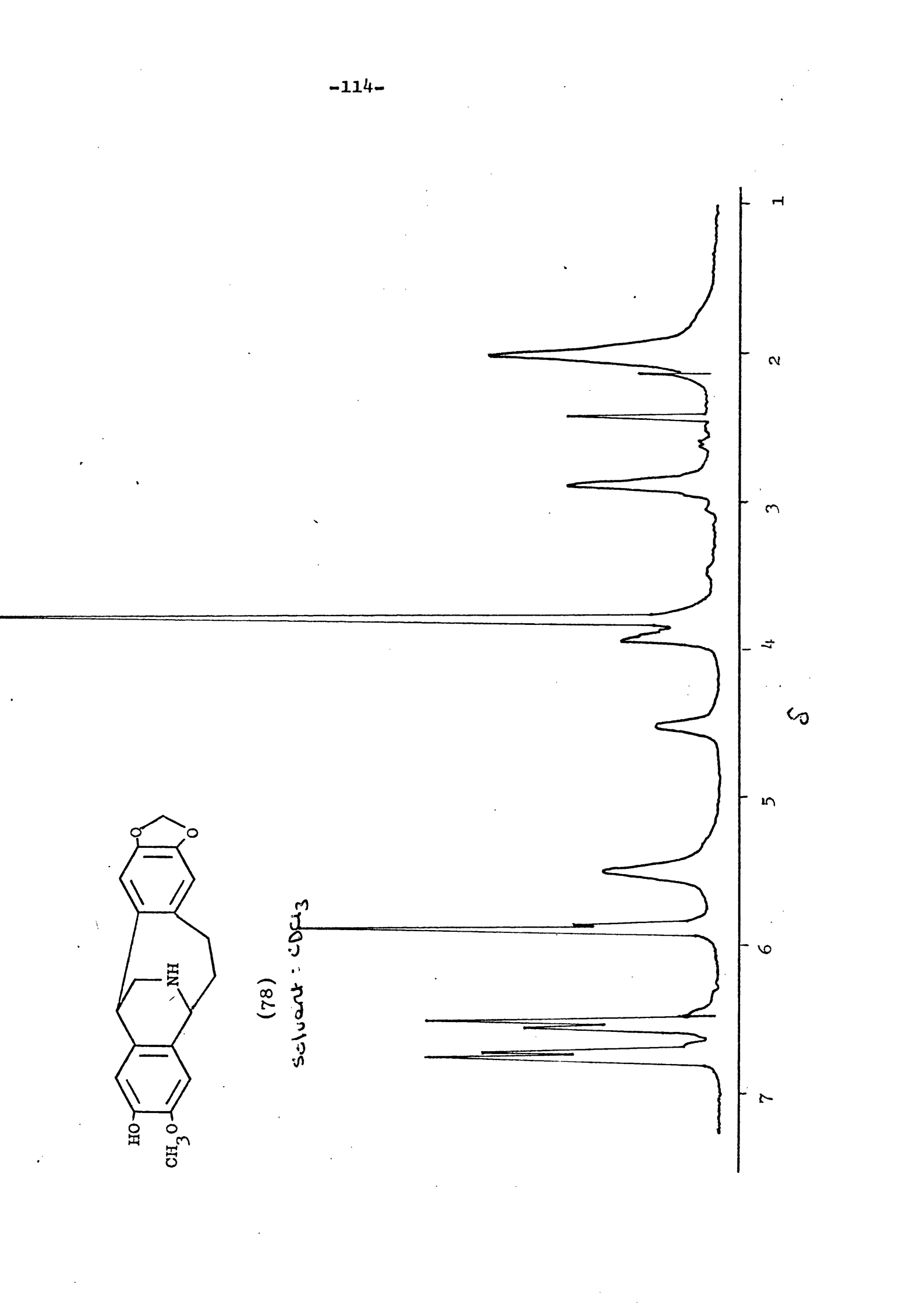


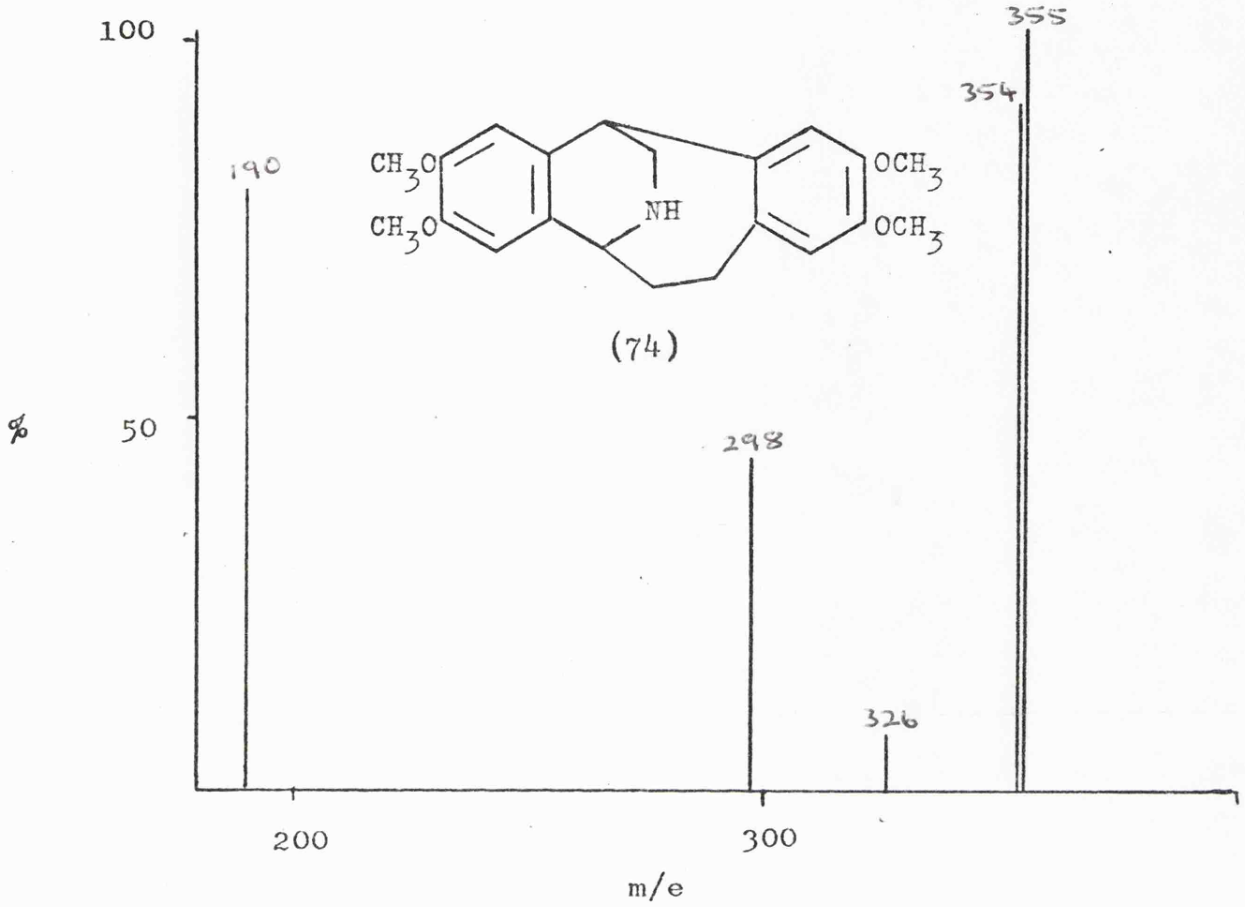
(76)

Solvant : $COCl_3$

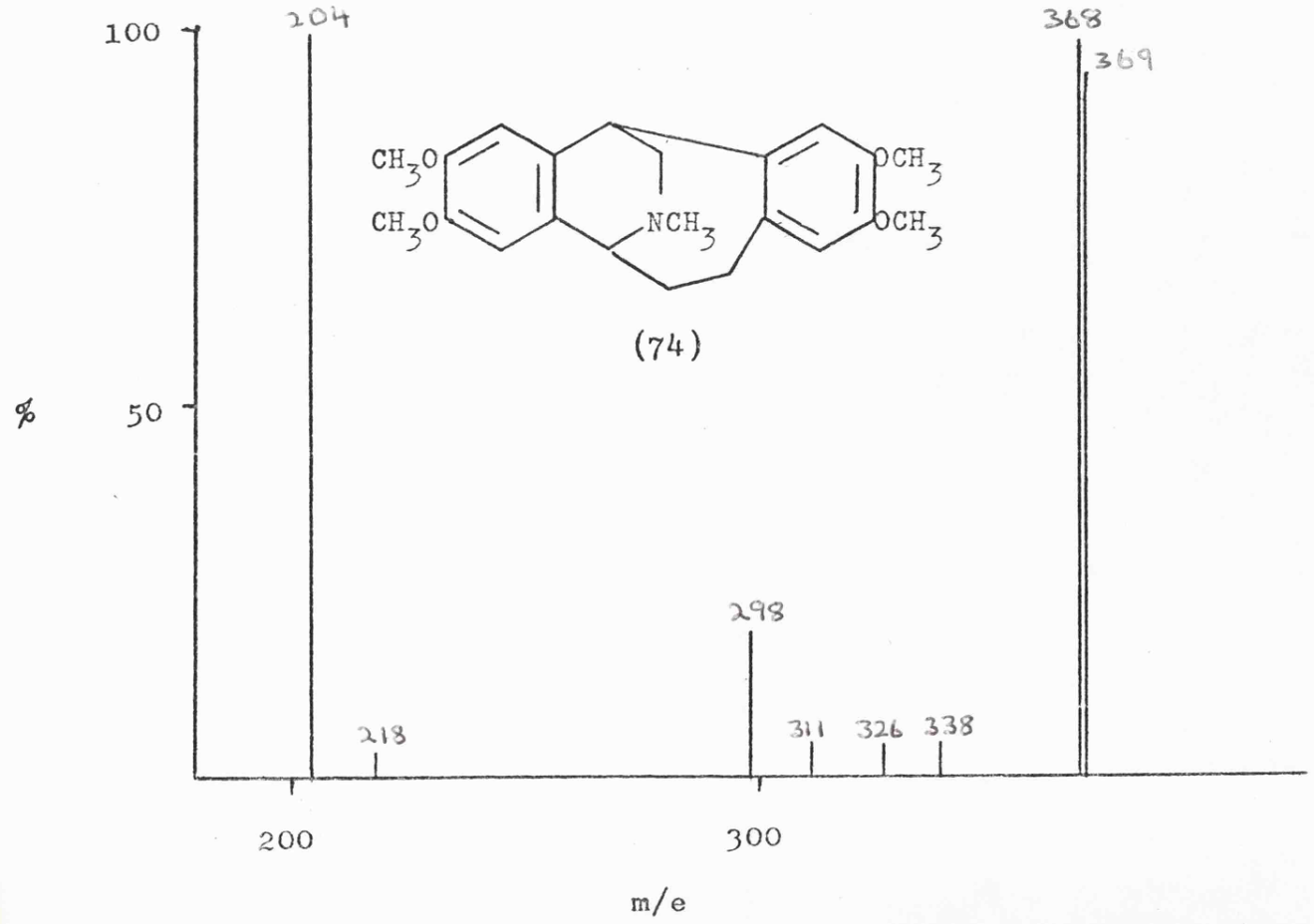

+ D_2O
1
2
3
4
5
6
7
δ
$PhCH_2O$
CH_3O
CH_3O
OCH_3
NH
O
O
(77)
Solvent : $CDCl_3$


0.0
0.5
1.0
1.5
A
200
250
300
350
λ (nm)
HO
CH3O
NH
O
O
(78)
----- + NaOH
Solvent: EtOH

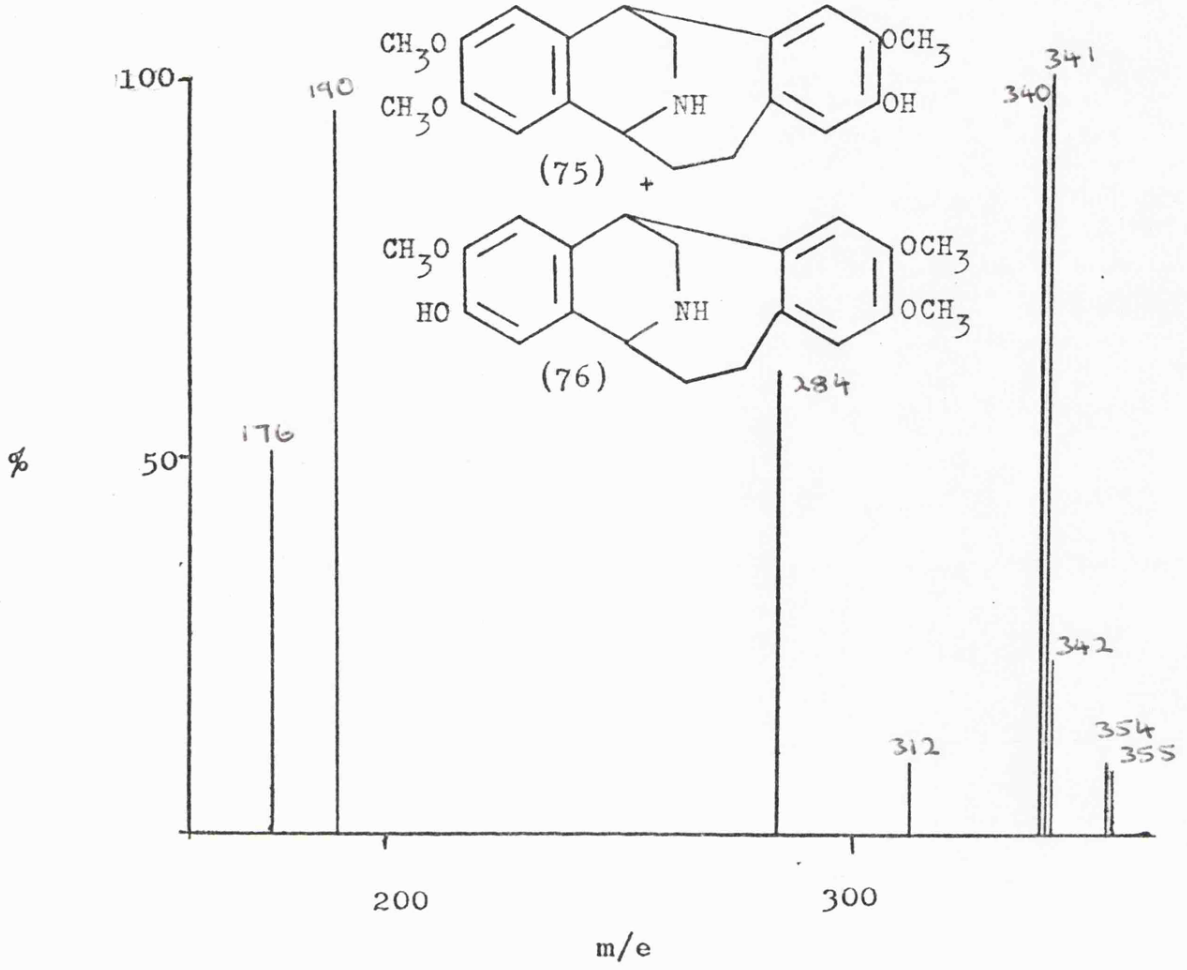

HO
CH_3O
NH
O
O
(78)
Solvent : $CDCl_3$
1
2
3
4
5
6
7
δ

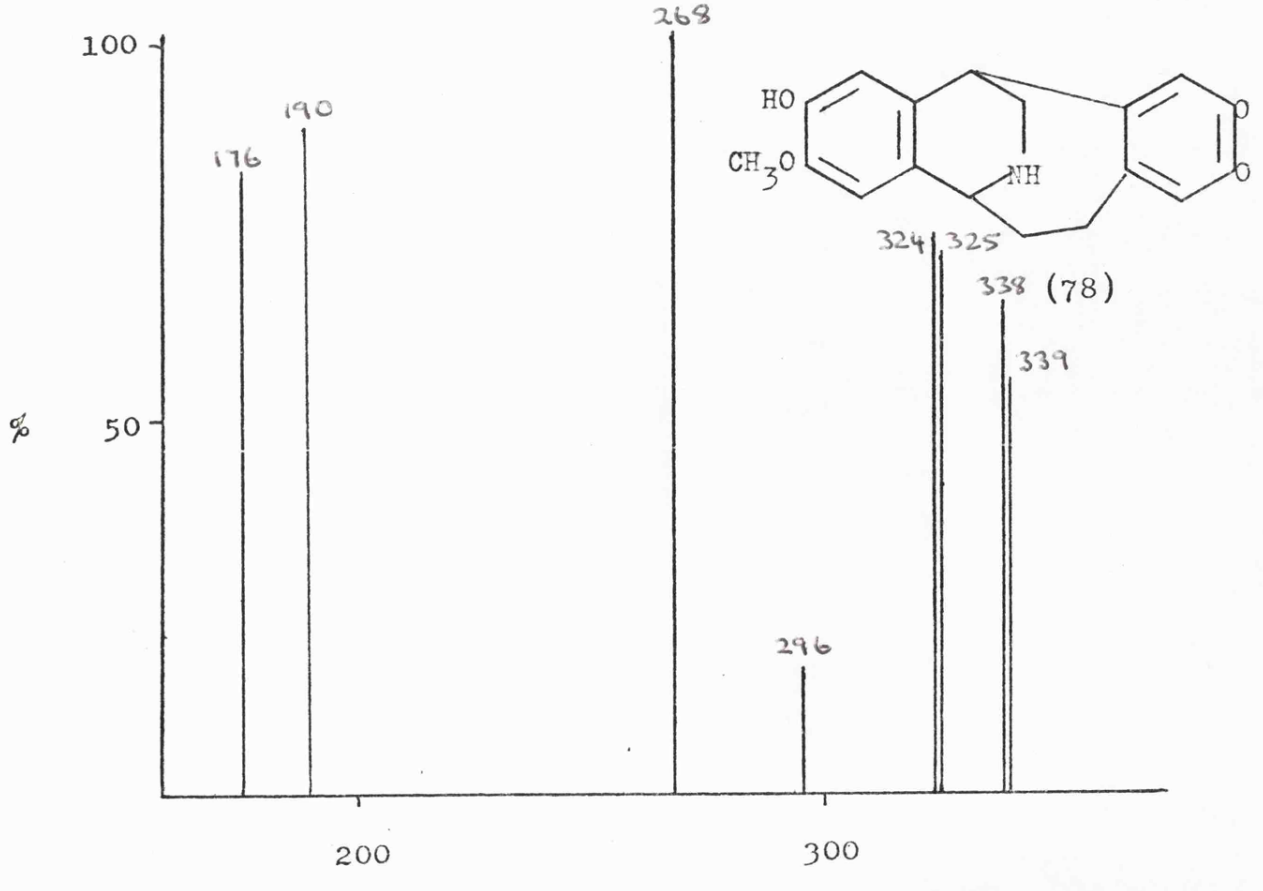

100
%
50
190
298
326
354
355
200
300
m/e
CH3O
CH3O
OCH3
OCH3
NH

(74)


100
%
50
204
218
298
311
326
338
368
369
200
300
m/e
CH3O
CH3O
OCH3
OCH3
NCH3

(74)


100
50
%
190
176
284
312
340
341
342
354
355
200
300
m/e
CH3O
CH3O
OCH3
OH
NH
(75)
+
CH3O
HO
OCH3
OCH3
NH
(76)


100
50
%
176
190
268
296
324
325
338
339
(78)
200
300
m/e
HO
CH3O
NH
O
O

REFERENCES

1. M. Shamma, "The Isoquinoline Alkaloids", Academic Press, New York, NY, 1972.
2. T. Kametani and K. Fukumoto, M.T.P. International Review of Science, Organic Chemistry Series One, Edited by K. Wiesner, Vol. 9, Chapter 6.
3. Chemical Society Specialist Periodical Reports, "The Alkaloids" Vol. 1, p. 120; Vol. 3, p. 163.
4. A.R. Battersby, R.B. Herbert, L. Mo and F. Santavy, J. Chem. Soc. (C) 1739 (1967).
5. A.R. Battersby, R. Binks, J.J. Reynolds and D.A. Yeowell, J. Chem. Soc., 4257 (1964).
6. E. Leete, Tetrahedron Letters, 333 (1965).
7. A.R. Battersby, R.B. Herbert, E. McDonald, R. Ramage and J.H. Clements, Chem. Commun, 603 (1966).
8. A.R. Battersby, Pure Appl. Chem. 14, 117 (1967).
9. A.C. Barker, A.R. Battersby, E. McDonald, R. Ramage and J.H. Clements, Chem. Commun, 390 (1967).
10. A.R. Battersby, P. Böhler, M.H.G. Munro and R. Ramage, Chem. Commun. 1066 (1969).
11. A. Brossi and F. Burkhardt, Helv. Chim. Acta, 44, 1558 (1961).
12. A.R. Battersby and T.P. Edwards J. Chem. Soc., 1214 (1960).
13. A. Rheiner, Jr., and A. Brossi, Experentia, 20, 488 (1964).
14. A. Brossi, J. O'Brien and S. Teitel, Helv. Chim. Acta., 52, 678 (1969).

15. A. Brossi and S. Teitel, Helv. Chim. Acta., 52, 1228 (1969).

16. T. Kametani, F. Satoh, H. Yagi and K. Fukumoto, J. Chem. Soc., (C), 382 (1970).

17. A.W. Sangster and K.L. Stuart, Chem. Rev., 65, 69 (1965).

18. L. Hruban and F. Santavy, Coll. Czech. Chem. Commun., 32, 3414 (1967).

19. A.R. Battersby, R.B. Herbert and F. Santavy, Chem. Commun., 415 (1965).

20. A.R. Battersby, R.B. Herbert, K. Pijewska and F. Santavy, Chem. Commun., 228 (1965).

21. A.F. Beecham, N.K. Hart, S.R. Johns and J.A. Lamberton, Aust. J. Chem., 21, 2829 (1968).

22. S.R. Johns, C. Kowala, J.A. Lamberton, A.A. Sioumis and J.A. Wunderlich, Chem. Commun., 1102 (1968).

23. J.S. Fitzgerald, S.R. Johns, J.A. Lamberton and A.A. Sioumis, Aust. J. Chem., 22, 2187 (1969).

24. S.R. Johns, J.A. Lamberton and A.A. Sioumis Aust. J. Chem., 22, 2219 (1969).

25. A. Brossi, J. Wursch and O. Schnider, Chimia 12, 114 (1958).

26. A. Brossi, H. Besendorf, B. Pellmont, M. Walter and O. Schnider, Helv. Chim. Acta., 43, 1459 (1960).

27. Hoffmann-La Roch Inc. U.S. Pat. 3067203 (1962).

28. A. Brossi, H. Besendorf, L.A. Pirk and A. Rheiner, Med. Chem., 5, 281 (1965).

29. T. Kametani and S. Takano, Tetrahedron Letters, 121 (1968), T. Kametani, S. Takano and K. Haga, Chem. Pharm.

Bull., 16, 663 (1968).

30. T. Kametani, S. Takano and T. Kobari, J. Chem. Soc., (C), 9 (1969).

31. T. Kametani, M. Koizumi and K. Fukumoto, J. Chem. Soc., (C), 1792 (1971), J. Org. Chem., 36, 3729 (1971).

32. T. Kametani, Y. Satoh, S. Shibuya, M. Koizumi and K. Fukumoto, J. Org. Chem., 36, 3733 (1971).

33. T. Kametani and M. Koizumi, J. Chem. Soc. (C)., 3796 (1971).

34. A.R. Battersby, R.B. Bradbury, R.B. Herbert, M.H.G. Munro and R. Ramage, Chem. Commun., 450 (1967).

35. T. Kametani, F. Satoh, H. Yagi and K. Fukumoto, J. Org. Chem., 33, 690 (1968).

36. A.R. Battersby, E. McDonald, M.H.G. Munro and R. Ramage, Chem. Commun., 934 (1967).

37. T. Kametani, K. Fukumoto, H. Yagi and F. Satoh, Chem. Commun., 878 (1967).

38. T. Kametani, F. Satoh, H. Yagi and K. Fukumoto, Chem. Commun., 1103 (1967).

39. T. Kametani, F. Satoh, H. Yagi and K. Fukumoto, J. Chem. Soc. (C)., 1003 (1968).

40. T. Kametani, H. Yagi, F. Satoh and K. Fukumoto, J. Chem. Soc. (C)., 221 (1968).

41. T. Kametani, K. Fukumoto, T. Hayasaka, F. Satoh and K. Kigasawa, J. Chem. Soc. (C)., 4 (1969).

42. T. Kametani and F. Satoh, Chem. Pharm. Bull., 17, 814, (1969).

43. T. Kametani, T. Sugahara, H. Sugi, S. Shibuya and K. Fukumoto, Tetrahedron, 27, 5993 (1971).

44. S. Ishiwata and K. Itabura, Chem. Pharm. Bull., 17, 2261, (1961).

45. W.V. Curran, Chem. Commun., 478 (1971).

46. T. Kametani and K. Fukumoto, J. Chem. Soc. (C)., 2156 (1968).

47. A. Brossi, A.I. Rachlin, S. Teitel, M. Shamma and M.J. Hillman, Experentia, 24, 766 (1968).

48. T. Kametani, T. Terui, T. Ogino and K. Fukumoto, J. Chem. Soc. (C)., 874 (1969).

49. F.R. Stermitz and D.K. Williams, J. Org. Chem., 38, 2099 (1973).

50. T. Richardson, R. Robinson and E. Seijo, J. Chem. Soc., 835, (1937).

51. G. Buchi, R.E. Manning and S.A. Monti, J. Am. Chem. Soc., 85, 1893 (1963).

52. D.W. Thomas and K. Biemann, J. Am. Chem. Soc., 87, 5447 (1965).

53. S.F. Dyke and A.C. Ellis, Tetrahedron, 27, 3803 (1971).

CHAPTER 3

VANADIUM OXYTRIFLUORIDE AND ITS APPLICATION TO THE SYNTHESIS OF NOVEL ISOQUINOLINE DERIVATIVES

INTRODUCTION

Oxidative Coupling

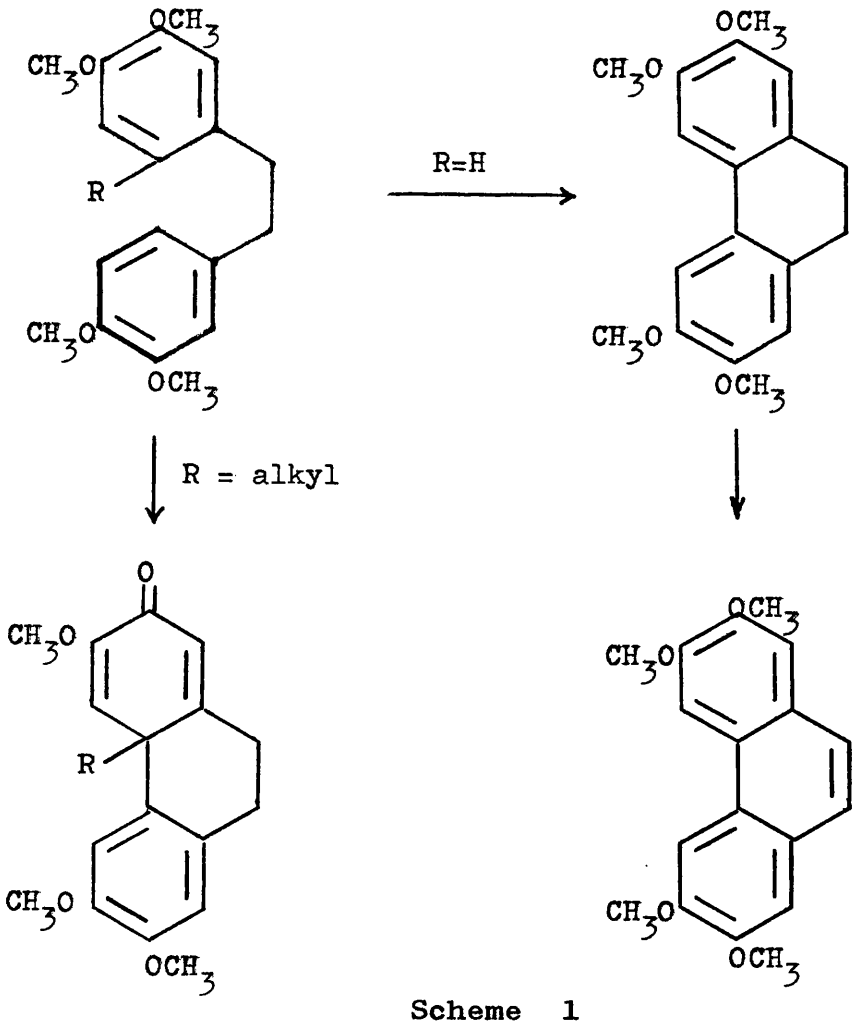
Intramolecular oxidative coupling of phenols plays an important role as a mode of carbon-carbon bond formation in the biosynthesis and synthesis of complex alkaloids and other polycyclic compounds[1,2]. In the field of isoquinoline alkaloids biosynthetic pathways to a variety of the alkaloid groups, for example, aporphines, morphines, proaporphines, cularines and bisbenzylisoquinolines[3], involve phenol oxidative coupling as a key reaction. Full realization of the synthetic potential of this type of reaction has been limited by the low yields usually encountered when the coupling reaction is carried out in the laboratory. The major problems associated with making this approach synthetically useful are: (a) generating the electron-deficient intermediate under conditions that minimise polymerisation resulting from intermolecular coupling of either the substrate or the intramolecularly coupled product and (b) controlling the sites of bond formation to give the product of desired structural type and substitution pattern.

The nature of the necessary electron-deficient intermediate depends on the type of substrate. In the case of diphenolic substrates, which are almost invariably involved in the biosynthetic process, the required intermediate has been assumed to be a diphenoxy diradical. Monophenolic substrates have been shown not to undergo intramolecular coupling when a phenoxy radical intermediate is generated[4], the desired coupling reaction in this case presumably requires

a more electrophilic phenoxy cation or cation radical (protonated phenoxy radical). Finally, oxidative coupling of non phenolic substrates requires cation radical intermediates.

Electrochemical Oxidation

Electrochemical oxidation is a useful method for biaryl coupling of phenols and phenol ethers. Simple methoxy derivatives of bibenzyl undergo intramolecular coupling to afford either dihydrophenanthrenes or the completely aromatic compounds in good yields by electrolysis.[5]



Scheme 1

Alkoxybibenzyl compounds with an electron donating substituent ortho to the ethylene link and para to a methoxy group give rise to dienones[6,7] (Scheme I). Several examples of the anodic oxidation of 1-benzylisoquinoline alkaloids to give morphinandienones have been reported[8].

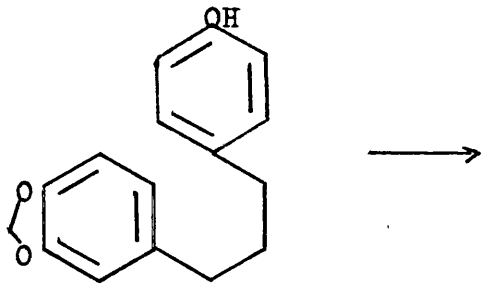
The principal advantage of the electrochemical method over other oxidation methods is the fact that the oxidation potential can be accurately controlled and can be chosen to carry out a desired reaction. Of course this method only works if the product is less easily oxidized than the starting material.

Chemical Oxidative Coupling

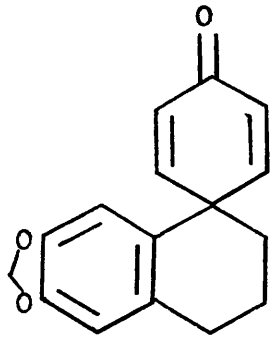
The classical work on the use of chemical reagents to effect phenolic coupling has been extensively reviewed[1]. Recently a number of reports describing efficient intramolecular oxidative aryl-aryl coupling of both phenolic and non phenolic substrates using a variety of newer chemical reagents have appeared. These newer reagents have been successfully used in the synthesis of a number of natural products, particularly isoquinoline alkaloids of the aporphine, proaporphine, homoaporphine and homoproaporphine types.

Schwartz et al reported[9] that oxidation of the diaryl propane (1) with one molar equivalent of thallium trifluoracetate in anhydrous CH_2Cl_2 afforded the dienone (2) in 87% yield. The method was extended to the synthesis of the Amaryllidaceae alkaloid (±)-oxocrinine (5), by oxidation of the N-trifluoracetyl norbelladine derivative (3) and hydrolysis of the resultant dienone (4). Also described

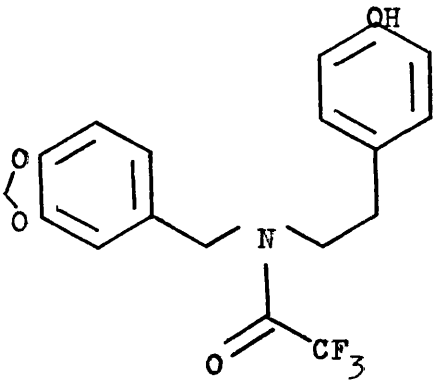
was the synthesis of the colchicine precursor O-methyl androcymbine (7) in 20% yield by oxidation of the protected phenethylisoquinoline (6) followed by removal of the blocking group.



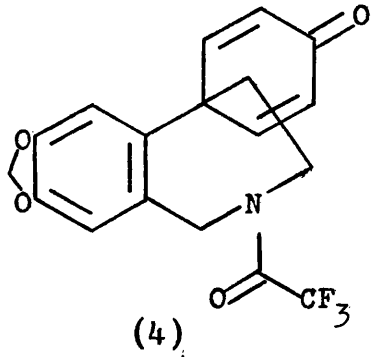
(1)



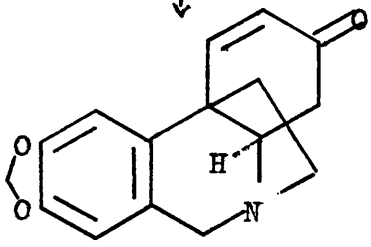
(2)



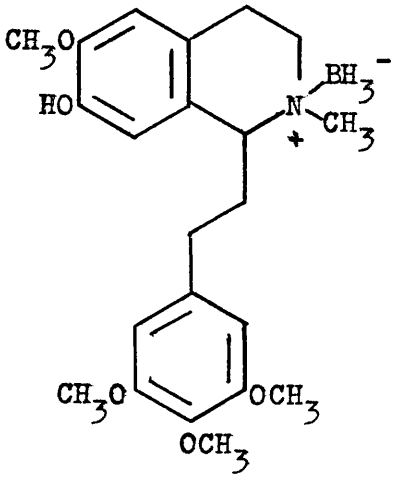
(3)



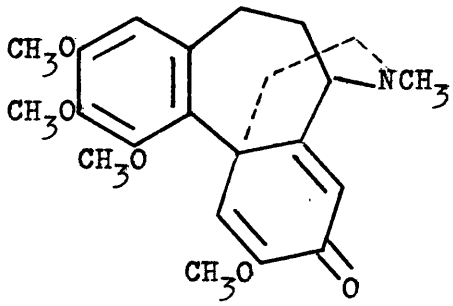
(4)



(5)

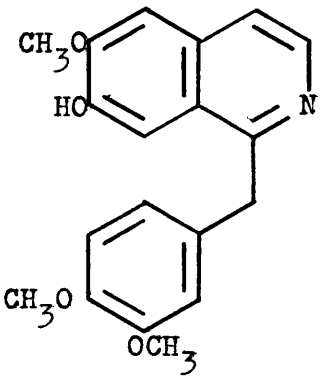


(6)

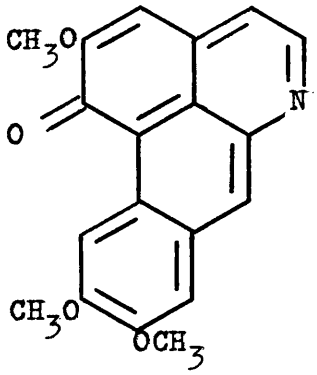


(7)

Kupchan and Liepa found that treatment of the 1-benzylisoquinoline (8) with a variety of oxidants afforded the quinonoid oxoaporphine (9)[10] (table I).



(8)



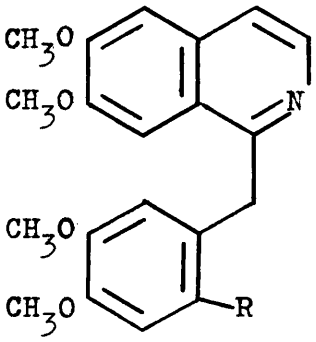
(9)

Oxidant	Medium	% Yield
$Ce(SO_4)_2$	10%aqH_2SO_4	25
$Co(OH)_3$	10%aqH_2SO_4	15
MnO_2	CF_3CO_2H	30
CrO_3	AqH_2SO_4-HOA_c	25
$Tl(CF_3CO_2)_3$	CF_3CO_2H	12
Pb_3O_4	CF_3CO_2H	22
VOF_3	CF_3CO_2H	59
$MoOCl_4$	CF_3CO_2H-$CHCl_3$	62

Table I

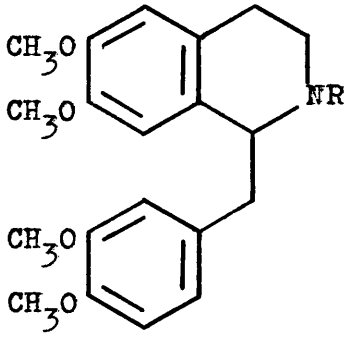
In a subsequent publication[11] Kupchan reported the first examples of chemical oxidative coupling of non phenolic substrates. Treatment of papavarine (10) with VOF_3 in TFA afforded an 80% yield of the aryl to aryl intermolecularly coupled product (11). Oxidation of (±)laudanosine (12a) with VOF_3 afforded (±) glaucine (13a) in 43% yield, whereas

oxidation of (±) N-formyl-norlandanosine (12b) afforded (±)-N-formylnorglaucine (13b) and (±) spirodienone (14) in yields of 6% and 55% respectively.



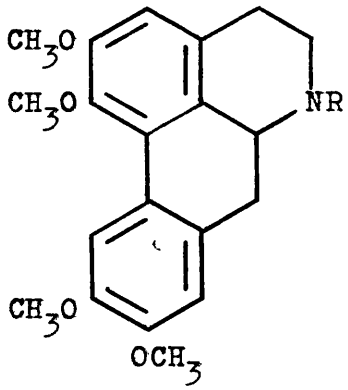
10, R = H

11, R = 6' - papaveryl



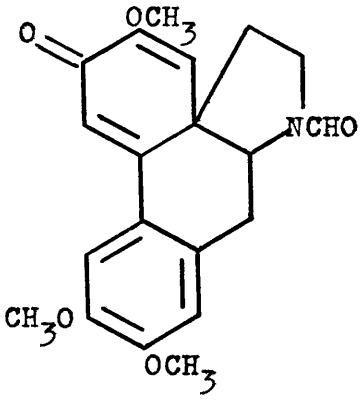
12(a) R = CH_3

12(b) R = CHO



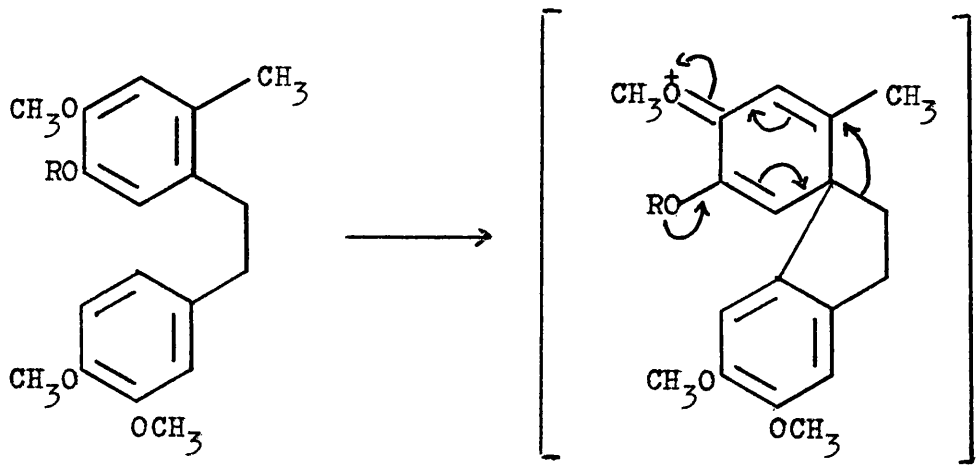
13(a) R=CH_3

13(b) R=CHO



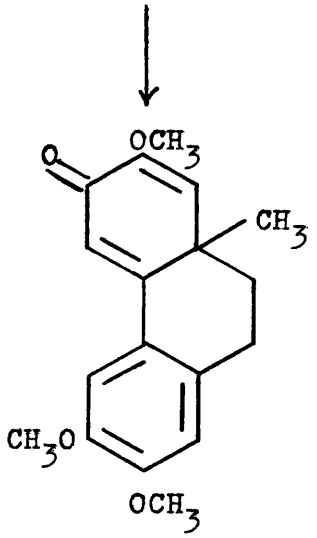
(14)

In an extension of these studies[12] Kupchan found that upon oxidation with VOF_3, the bibenzyls (15a) and (15b), both afforded the same dihydrophenanthrone (17), thus indicating that the coupling reactions proceed via the five membered ring spiro intermediates (16a) and (16b) (scheme 2). The similarity between the rearrangement of (16a) and (16b) to (17) and the acid-catalysed rearrangement of proerythrinandienones to neospirinedienones (21)[13],



15(a) R = CH_3
15(b) R = C_2H_5

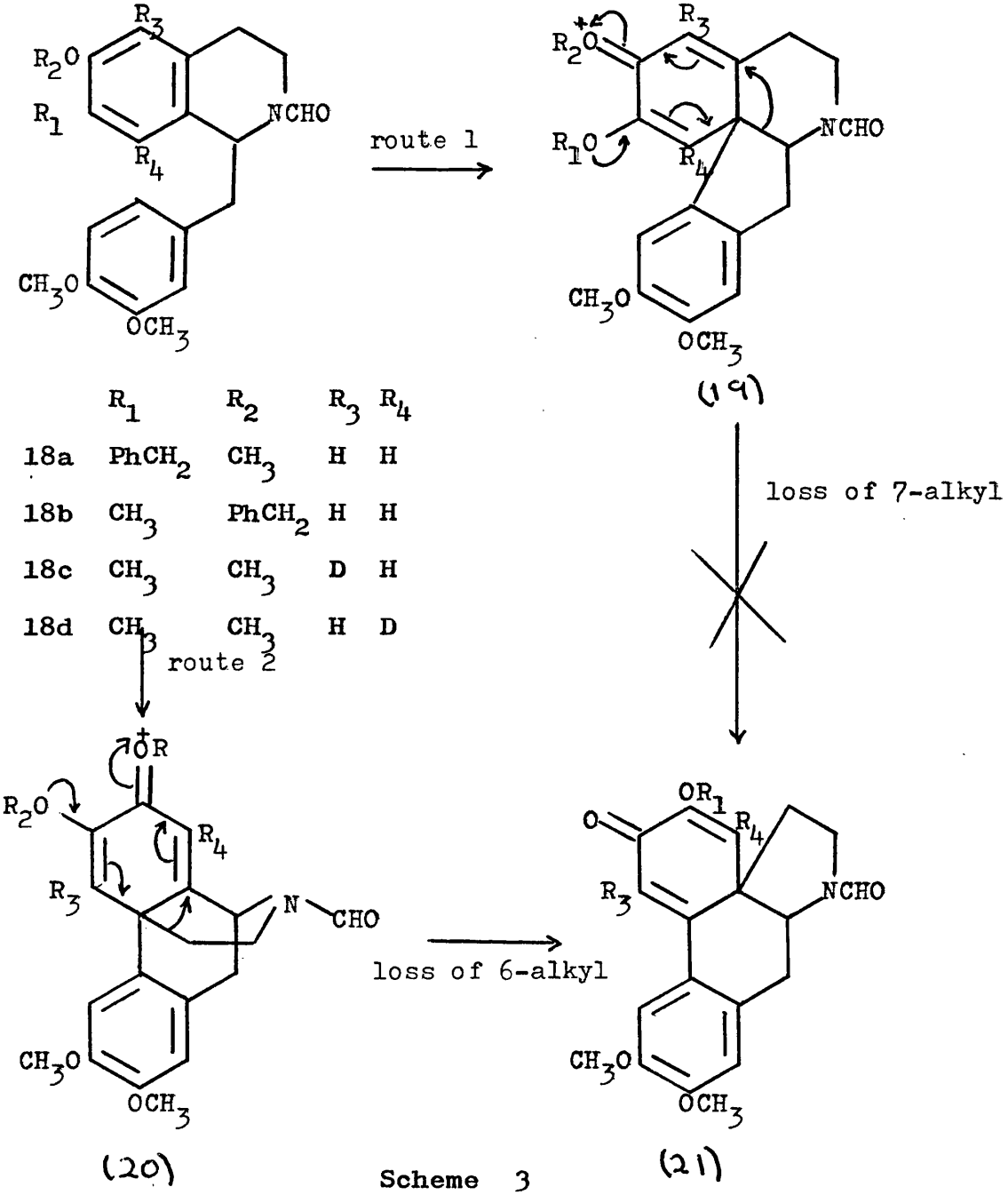
16(a) and (b)



(17)

Scheme 2

led the authors to consider the possibility that the formation of the neospirinedienone (14) by VOF_3-TFA oxidation of N-formylnorlaudanosine may occur via the route 1 (scheme 3). However studies of the oxidation of the N-acyl-1-benzyl-1,2,3,4-tetrahydroisoquinolines (18a-d) showed that coupling occurred via the morphinandienone type intermediate (20), route 2 (scheme 3).



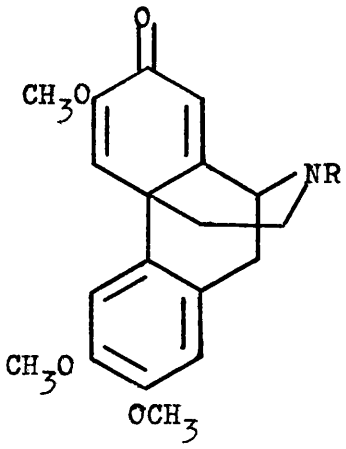
	R_1	R_2	R_3	R_4
18a	$PhCH_2$	CH_3	H	H
18b	CH_3	$PhCH_2$	H	H
18c	CH_3	CH_3	D	H
18d	CH_3	CH_3	H	D

(19) (20) (21)

Scheme 3

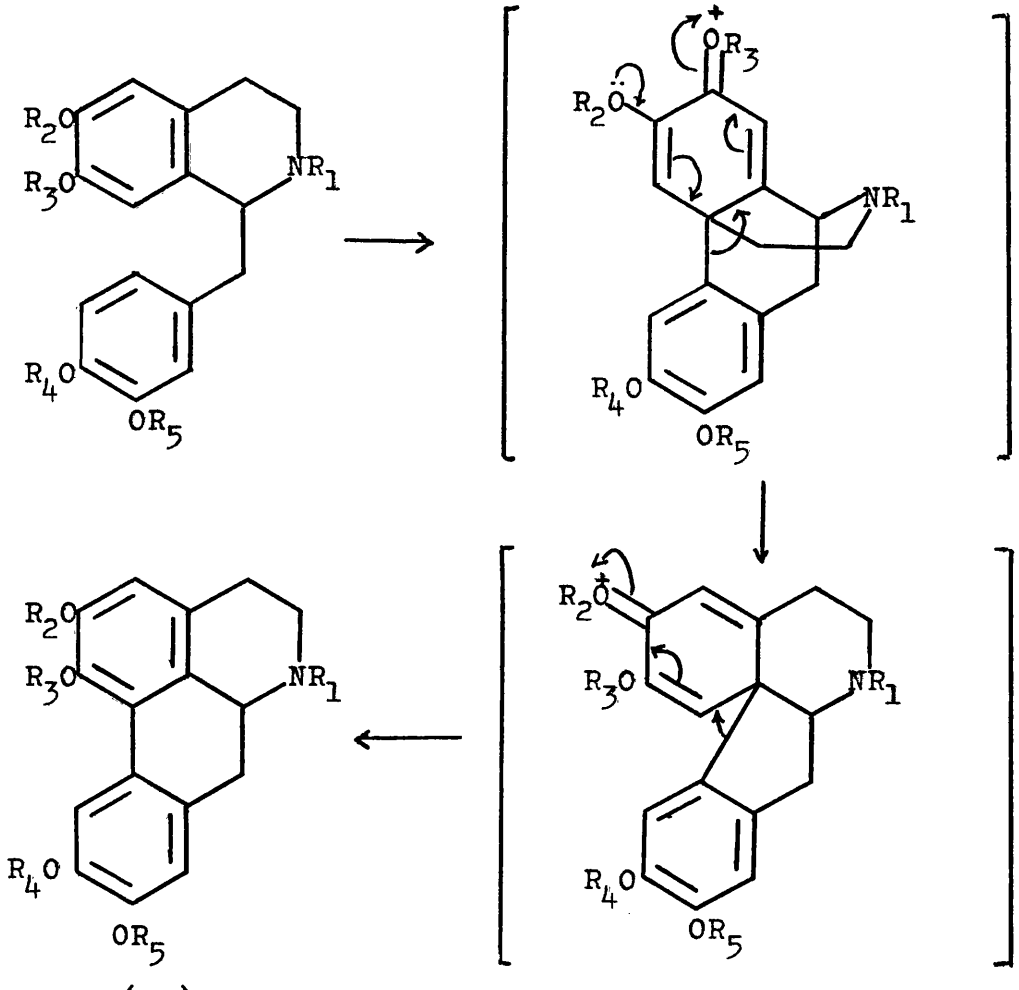
Evidence for the postulated facile acid catalysed rearrangement of (20, $R_1=R_2=OCH_3$) to the acylneospirinedienone (14) was provided by a study of the chemistry of the N-formylmorphinandienone (22a) produced by electrooxidative coupling of (12b) in HBF_4. Treatment of (22a) with anhydrous methanolic HCl afforded the dimethyl ketal of (14).

Treatment of (22a) with HBF_4 gave (21, R_1=R_3=R_4=H) in 74% yield and methylation then gave (14) in 31%[12].



22(a) R = CHO (b) R = CH_3

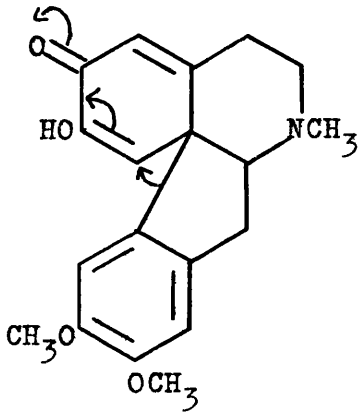
Kupchan further postulated the intermediacy of morphinandienones in the chemical and anodic oxidation of 1-benzyltetrahydroisoquinolines to aporphines[14]. (Scheme 4)



(23)

Scheme 4

Evidence in support of this postulate was provided by acid treatment of (±)-O-methylflavinantine (22b) which afforded (23, $R_1=R_4=R_5=CH_3$, $R_2=R_3=H$) in 89% yield, presumably via the proerythrinandienone (24).

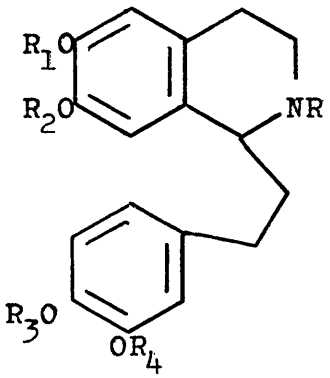


(24)

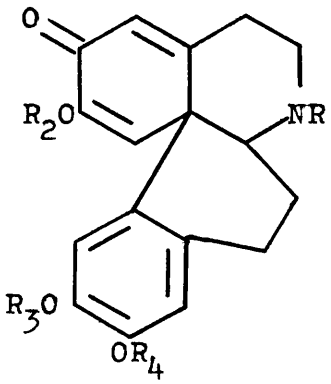
Hence Kupchan concluded that the acid catalysed rearrangement of morphinandienones follows two principal routes. In the case of substrates and conditions which enhance the participation of the nitrogen lone pair, aryl migration to proerythrinedienones followed by rearrangement to aporphines is favoured. In contrast, acid catalysed rearrangements which involve minimal nitrogen participation (e.g., with boron trifluoride salts or amide derivatives) result in alkyl migration to yield neospirine derivatives.

In further publications[15,16] Kupchan reported studies of the oxidation of non phenolic and phenolic 1-phenethyl-tetrahydroisoquinolines with VOF_3. Oxidation of (±)-N-trifluoracetylhomonorlaudanosine (25a) in CH_2Cl_2 and TFA at -10° with VOF_3 in TFA for 10 minutes, followed by aqueous work up afforded homoproerythrinadienone (26a) 5%,

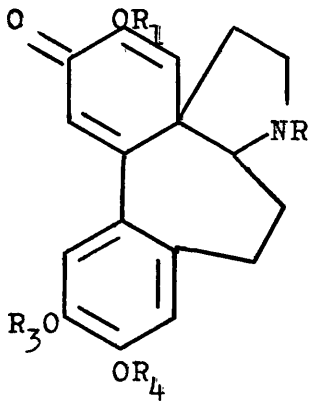
homoneospirinedienone (27a) 64%, homoaporphine (28a) 2%, and the aldehyde (29), 22%. Oxidation of the diphenolic compound (25b) afforded the homoproerythrinadienone (26b) in 78% yield. Upon treatment with BF_3-Et_2O in CH_2Cl_2 at room temperature for 24 hours the homoproerythrinadienone (26a) and homoneospirinedienone (27a) rearranged to the homoaporphines (28b) and (28c) respectively.



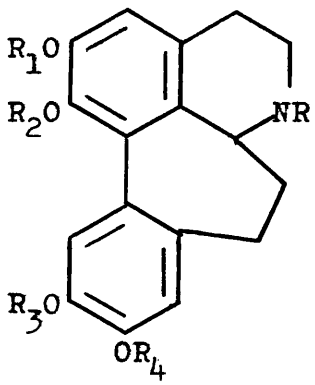
	R_1	R_2	R_3	R_4	R
25a	CH_3	CH_3	CH_3	CH_3	$COCF_3$
25b	H	CH_3	CH_3	H	$COCF_3$
25c	CH_2Ph	CH_3	CH_3	CH_3	$COCF_3$
25d	CH_3	CH_2Ph	CH_3	CH_3	$COCF_3$
25e	CH_3	H	H	CH_3	CH_3



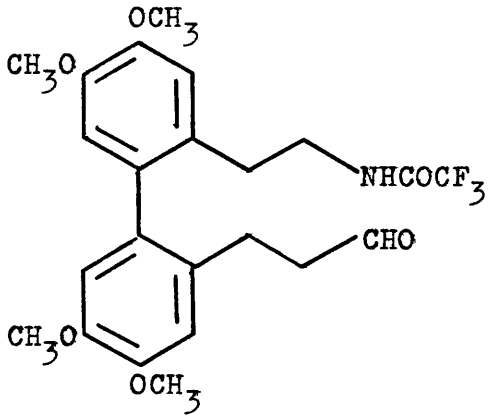
(26)



(27)



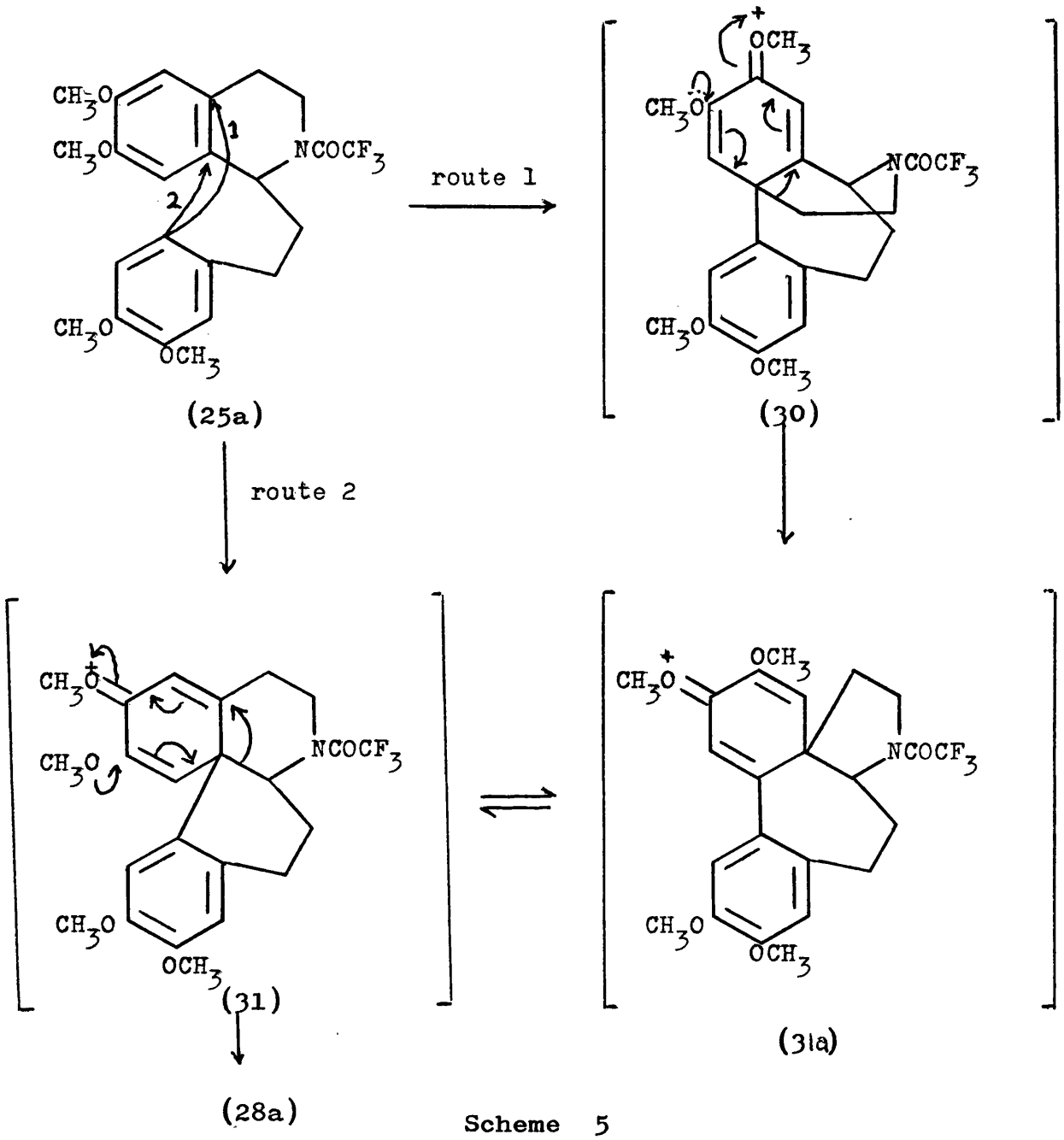
	R_1	R_2	R_3	R_4	R
28b	H	CH_3	CH_3	CH_3	$COCF_3$
28c	CH_3	H	CH_3	CH_3	$COCF_3$



(29)

To investigate the mechanisms of these reactions Kupchan studied the oxidation of the 6-benzyloxy (25c) and 7-benzyloxy (25d) analogues of N-trifluoracetyl-homonorlaudanosine. Oxidation of (25c) afforded (26a) (50%) and (27c) (42%) whereas (25d) gave (26d) (3%) and (27a) (60%) thus precluding route 1 (scheme 5) via homomorphinandienone intermediates e.g. (30), and confirming route 2 via homoproerythrinadienone intermediates such as (31). Furthermore Kupchan concluded that the homo-proerythrinadienone-type intermediates (31) and the homo-neospirinedienone-type intermediates (31a) were in equilibrium and that the high yields of (26a) and (27a) in the oxidations of (25c) and (25d) respectively, indicated shifts of equilibria due to easy cleavage of the benzyl groups from the corresponding benzyloxonium ions. This was confirmed by the isolation of (26a) 71% and (27a) 65% upon treatment of (25c) and (25d) respectively, with VOF_3-TFA for 1 hour.

That homoaporphines might be obtained directly from the phenethylisoquinolines if enough time were allowed for rearrangement of the corresponding homoproerythrinadienone

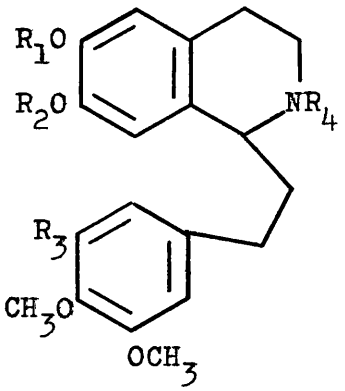


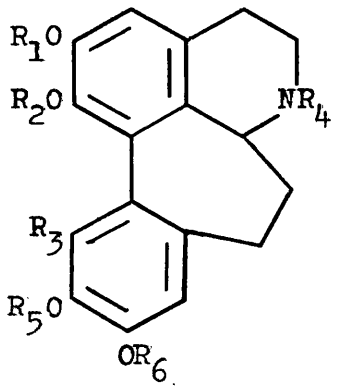
Scheme 5

and homoneospirinedienone intermediates, was confirmed by treatment of the phenethylisoquinolines (25a), (25c) and (25d) with VOF_3-TFA for several hours, whereupon the homoaporphines (28a), (28b) and (28c) were obtained in yields of 84%, 80% and 65% respectively.

In the case of the monophenolic compounds, oxidation of 7-hydroxy-1-lphenethyltetrahydroisoquinolines (32a-d) with VOF_3-TFA at -10 to 15° for 5-10 minutes afforded

the homoaporphines (33a-d) together with the homoproaporphines (34a-d)[16]. In the case of the N-trifluoracetyl compounds (32a) and (32c) the homoaporphine was the major product, whereas in the case of the N-methyl compounds (32b) and (32d), the major products were the homoproaporphines. No homomorphinandienones could be detected by thin layer chromatography in any of these experiments. The homoproaporphines (34a-d) underwent smooth dienone-phenol rearrangements upon treatment with BF_3-Et_2O in CH_2Cl_2 at room temperature to give the homoaporphines (33e-h) respectively. Kupchan concluded that the formation of homoaporphines (33a-d) from the phenethyltetrahydroisoquinolines (32a-d) proceeds via homoproaporphine-type intermediates (35a-d) and showed that the yields of the homoaporphines was increased by increasing the reaction time so as to allow time for rearrangement of the intermediates.

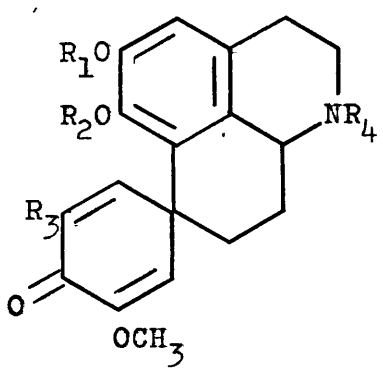




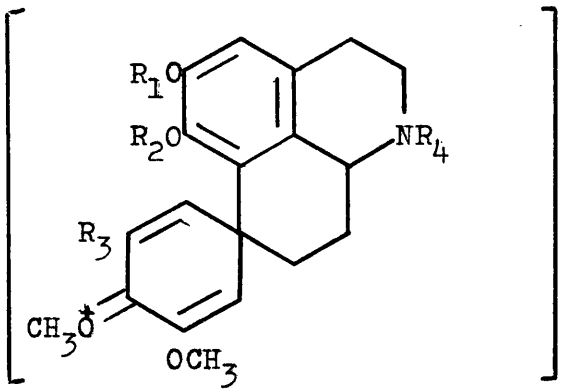
	R_1	R_2	R_3	R_4
32a	CH_3	H	H	$COCF_3$
32b	CH_3	H	H	CH_3
32c	CH_3	H	OCH_3	$COCF_3$
32d	CH_3	H	OCH_3	CH_3

33a-d $R_5 = R_6 = CH_3$

	R_1	R_2	R_3	R_4	R_5	R_6
33e	CH_3	H	H	$COCF_3$	CH_3	H
33f	CH_3	H	H	CH_3	CH_3	H
33g	CH_3	H	OCH_3	$COCF_3$	H	CH_3

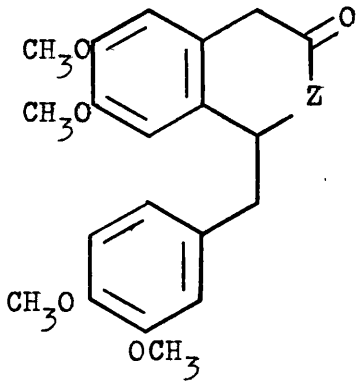


34 a - d



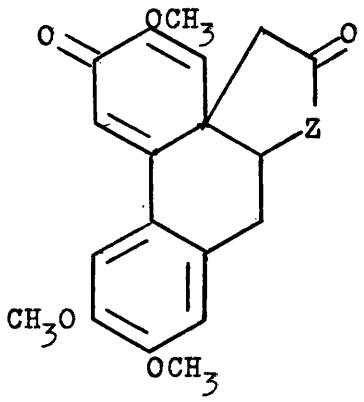
35 a - d

Elliot found[17] that oxidation of (36a) and (36b) electrolytically or with VOF_3 in dichloromethane TFA afforded the same dienones (37a) and (37b).



36a Z = O

36b Z = NCH_3



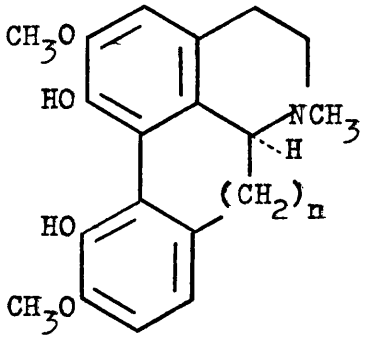
37a Z = O

37b Z = NCH_3

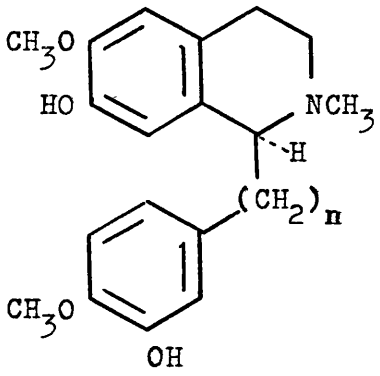
Schwartz et al reported[18] that vanadium oxytrichloride was an effective oxidant for the intramolecular oxidative coupling of a series of diphenolic, monophenolic and non-phenolic 1,3-diaryl propanes. Furthermore the fact that the oxidative coupling of the diphenolic substrates was unnaffected by added triethylamine or by changes in solvent

basicity, whereas the coupling of monophenolic and non-phenolic substrates was very sensitive to these factors, led them to propose that different mechanisms were operative in each case. They proposed that a radical intermediate was involved in the case of diphenolic substrates and that the unusually good yields of phenolic coupling might be due to some stabilization of the radical intermediates by complexation with vanadyl species. Such stabilization had been observed with hydroxy and hydroperoxy radicals in the presence of oxyvanadium ions[19]. The similarity in behaviour of $VOCl_3$ towards monophenolic and non-phenolic substrates, led them to propose that in both cases, two successive one electron oxidations are involved and that coupling occurs at the cation radical stage.

Syntheses of a number of isoquinoline alkaloids, involving the use of cuprous chloride and molecular oxygen in pyridine as an enzymic model to effect phenolic coupling, have been reported by Kametani and co-workers[20]. Treatment of (+) reticuline (38a) perchlorate afforded (+)-corytuberine (39a), (+) isoboldine (40a) and palladine (41a) in yields of 28%, 8% and 6% respectively. (±)-1,2,3,4-tetrahydro-7-hydroxy-1-(3-hydroxy-4-methoxyphenethyl)-6-methoxy-2-methylisoquinoline (38b) hydrochloride gave also ortho-ortho (racemate of (39b), 5%), ortho-para (racemate of (40b), 2%) and para-para (racemate of (41b), 2%) coupling products. These were the first reported examples of ortho-ortho oxidative coupling with chemical reagents.

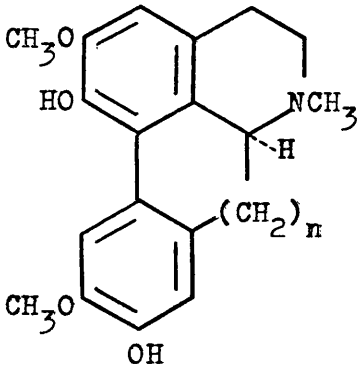


39 a, b

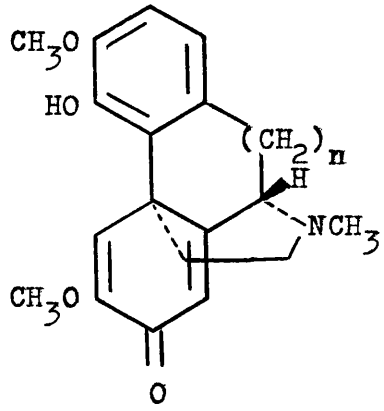


38a n = 1

38b n = 2



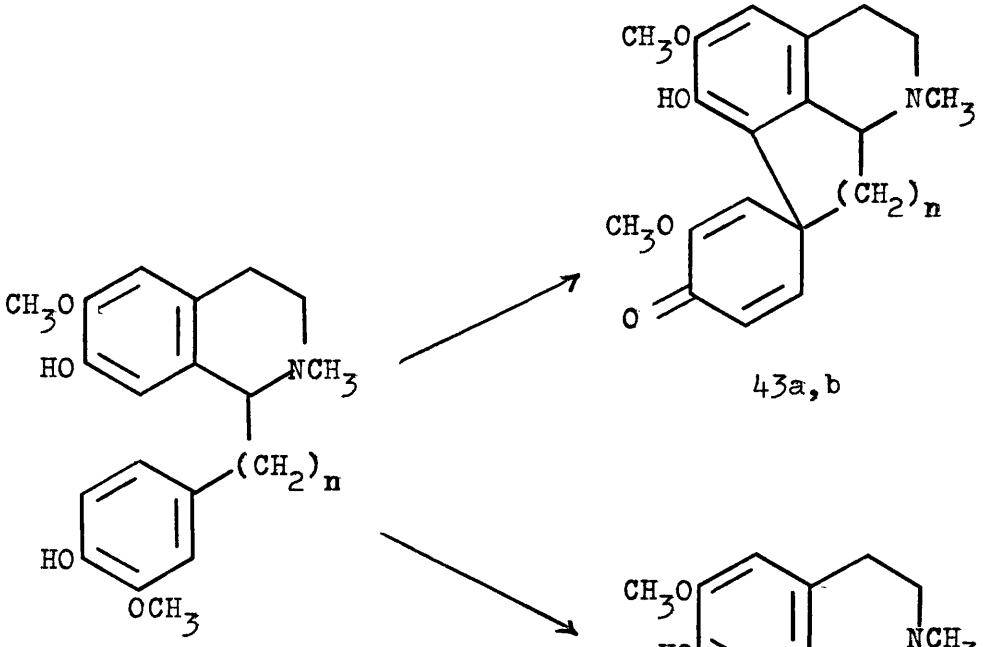
40 a, b



41 a, b

A similar reaction of (±)-orientaline (42a) perchlorate gave (±)-orientalinone (43a) and (±) isoorientalinone (44a) in yields of 19.4% and 6.5% respectively, while the racemic phenethylisoquinoline (42b) hydrochloride gave (±)-kreysiginone (43b) and its diastereomer (44b) in yields of 11.4% and 26.6% respectively.

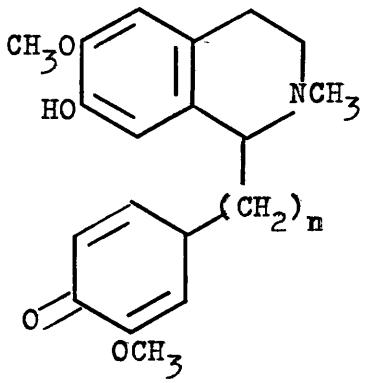
The use of divalent copper salts such as cupric chloride in place of cuprous chloride gave no oxidized products. However a mixture of cupric chloride and excess potassium superoxide in pyridine afforded the same oxidatively coupled products in approximately the same yields, as



42a n = 1

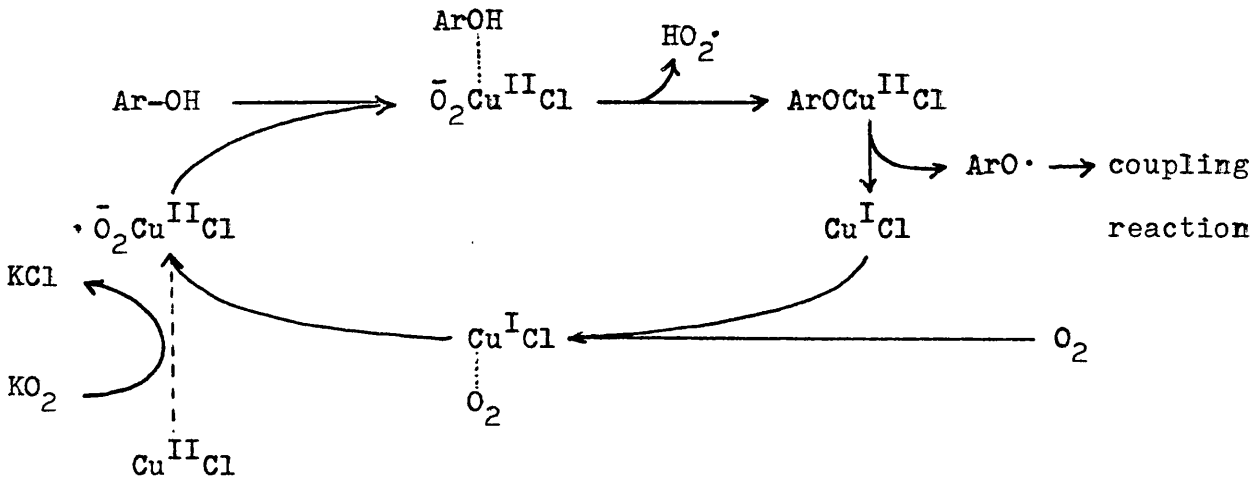
42b n = 2

43a,b



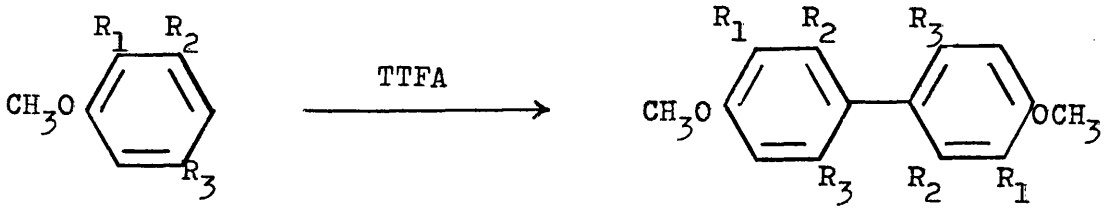
44a,b

obtained with the cuprous chloride and molecular oxygen in pyridine system. Hence Kametani proposed the mechanism shown in scheme 6, involving a cupric complex such as (45) for these reactions.



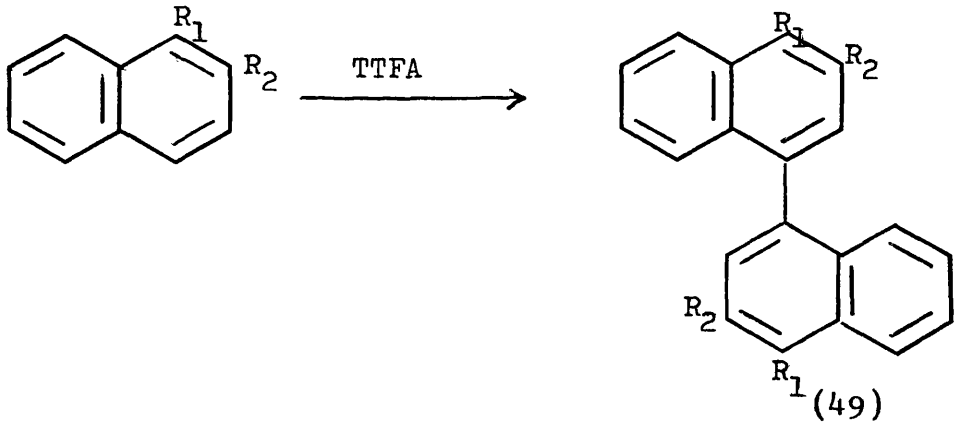
Scheme 6

Further reports on the use of thallium (III) trifluoroacetate (TTFA) as an effective reagent for oxidative coupling of aromatic compounds have recently appeared[21]. Treatment of a variety of aromatic substrates with TTFA in trifluoroacetic acid or acetonitrile containing borontrifluoride etherate was reported to result in smooth, rapid and direct oxidative coupling to give symmetrical biaryls in good yield. Thus the anisole derivatives 46a-f afforded the biaryls 47a-f and the naphthalene derivatives 48a-g were converted into the binaphthyls 49a-g.



(47)

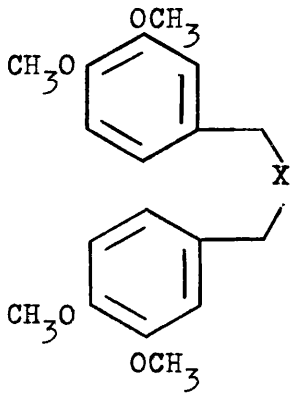
	R_1	R_2	R_3	Yield %
46a	CH_3O	H	Br	88
46b	CH_3O	H	I	89
46c	CH_3O	H	CH_3	74
46d	CH_3O	CH_3	Br	99
46e	CH_3	H	CH_3	60
46f	CH_3	CH_3	CH_3	74



(49)

	R_1	R_2	Yield %
48a	CH_3	H	93
48b	CH_3O	H	88
48c	CH_3O	CH_3	92
48d	CH_3O	Cl	82
48e	CH_3O	Br	81
48f	Br	H	87
48g	I	H	94

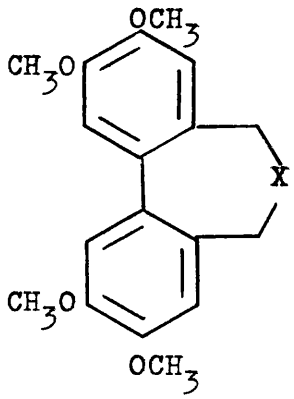
The effectiveness of the proceedure for intramolecular coupling was illustrated by conversion of 1,3-bis (3,4-dimethoxyphenyl)propane (50a) to the bridged biphenyl (51a) in 81% yield. The authors proposed a mechanism involving (a) reaction of TTFA with aromatic substrate and generation of the radical cation Ar^+, (b) reaction of this electrophile with the aromatic substrate and (c) oxidative aromatisation of the intermediate thus produced, by TTFA.



(50)

a X = CH_2

b X = O



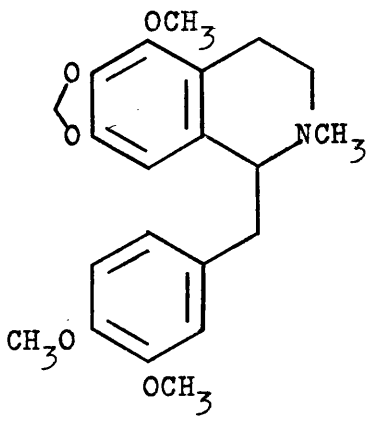
(51)

a X = CH_2

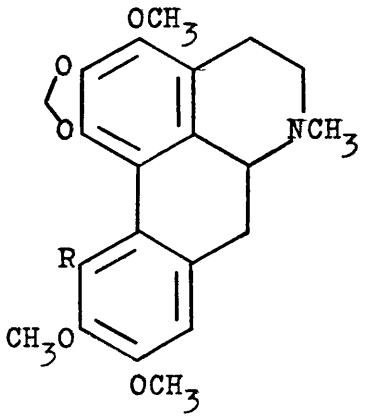
b X = O

In a subsequent publication[22] the same authors reported that the ether (50b) was smoothly coupled to 5,7-dihydro,-2,3,9,10-tetramethoxydibenzo [c,e] oxepin (51b) in 80% yield by treatment with TTFA. Thus showing that this oxidative coupling process could be extended to the synthesis of heterocycles. Furthermore, treatment of the 1-benzyl-tetrahydroisoquinoline (52) with TTFA at -40° afforded the aporphine (53a), in 46% yield, whereas

when the reaction was carried out at 0° the acetoxy aporphine (53b) was formed in 35% yield.



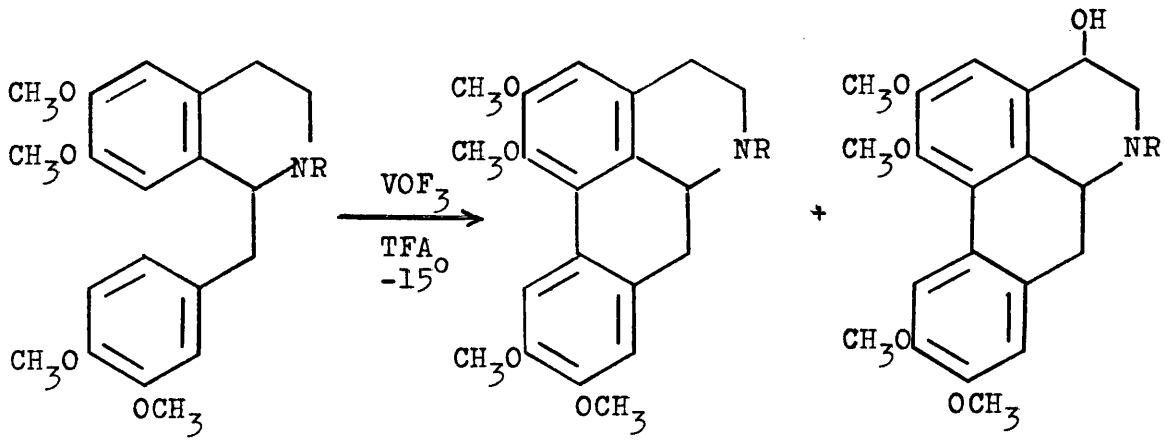
(52)



(53)

a R = H
b R = $OCOCH_3$

Hartenstein and Satzinger recently reported[23] that oxidation of (±) laudanosine (54a) with VOF_3 (2 mol. equiv.) in TFA at -15° afforded (±) cataline (4-hydroxy glaucine) (56a) in 40% yield together with small amounts of (±) glaucine (55a). Furthermore, they found that only one of the two possible diastereomeric pairs of (56a) had been formed. Similarly (±) tetrahydropapaverine (54b) afforded (±)-norglaucine (55b) and (±)-N-norcataline (56b) in yields of 30% and 38% respectively. Use of optically active (-)-tetrahydropapaverine led to (+)-N-norglaucine and (+)-N-norcataline. Treatment of (+)glaucine and (-)glaucine with VOF_3 afforded (+)cataline and (-)cataline respectively in 50 to 60% yields.



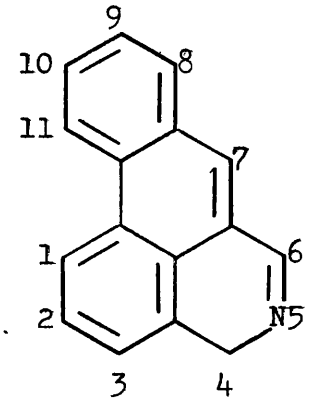
(54) (55a,b) (56a,b)

a R = CH_3

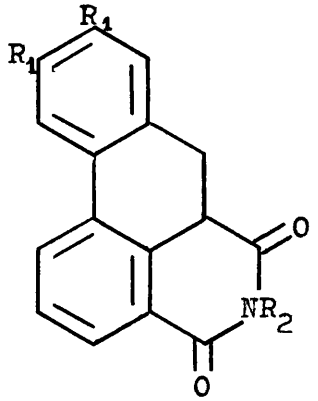
b R = H

The Dibenzy [de,g] isoquinoline system

The dibenzy [de,g] isoquinoline (5-azabenzanthrene) ring system (57) has been little studied. Certain derivatives of this system could be regarded as isomers of the aporphine alkaloids[3] and may exhibit interesting pharmacological activity. In recent years, previous workers in this laboratory have been examining possible synthetic routes to these compounds from the now readily available 4-benzylisoquinoline derivatives[24], with little success. At the time this work started, only two syntheses of the dibenzy [de,g] isoquinoline system had been reported.



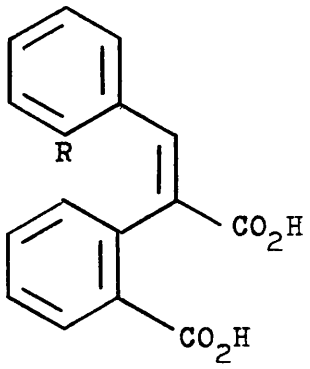
(57)



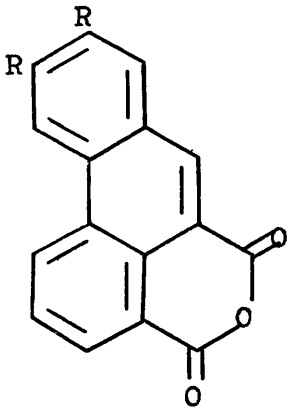
(58) a R_1=R_2=H

b R_1=OMe, R_2=Me

Pschorr prepared 4,6-diketodibenz [de,g] isoquinoline (58a) by condensing o-nitrobenzaldehyde with homophthalic acid, followed by hydrolysis to (59), reduction to (60) and cyclisation via the diazonium salt to yield (61a). Treatment with ammonia then afforded (58a) in 8% overall yield[25].

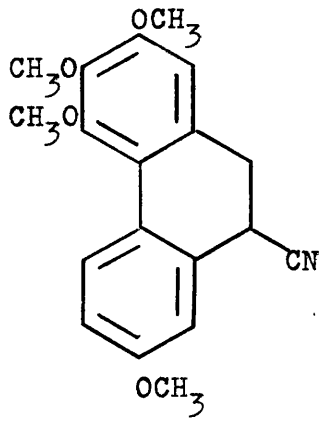


(59), R = NO_2
(60), R = NH_2

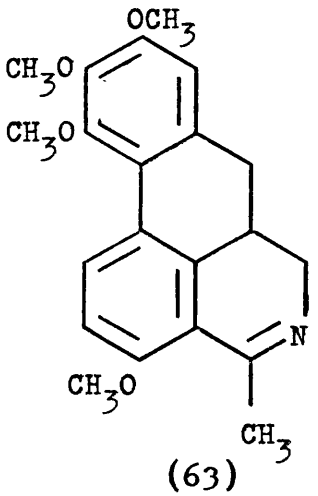


(61) a R = H
(61) b R = OCH_3

Cook et al prepared 3,9,10,11-tetramethoxy-4-methyl-7,7H-dibenz [de,g] isoquinoline (63) from the 9,10-dihydro-9-cyanophenanthrene (62). Reduction to the amine, followed by N-acetylation and cyclodehydration with P_2O_5 yielded (63)[26].

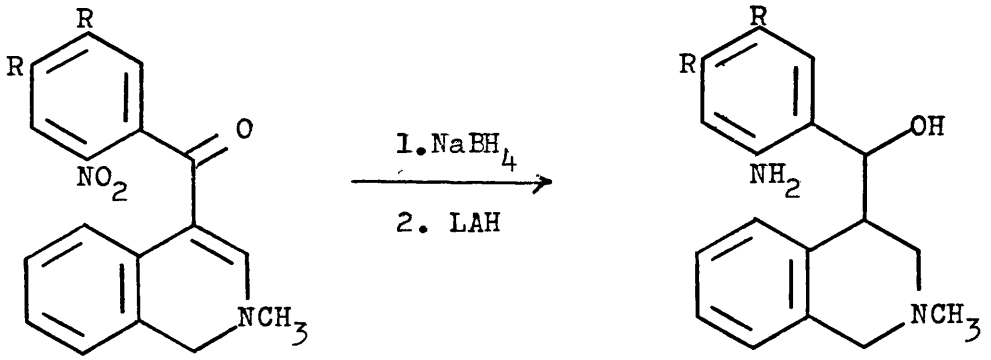


(62)



(63)

An alternative synthesis was reported from this laboratory[27] involving reduction of the 4-acyl-1,2-dihydroisoquinoline (64a) to give (65a) which upon Pschorr cyclisation and dehydration afforded the dibenz [de,g] isoquinoline (67a). The yield from isoquinoline methiodide was 4%. The low yield steps were the reduction of (64a) to (65a) and Pschorr cyclisation of (65a) to (66a). The structure of (67a) was confirmed by treating (61a) with methylamine followed by reduction with LAH.

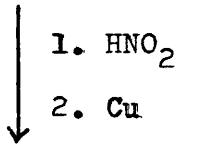


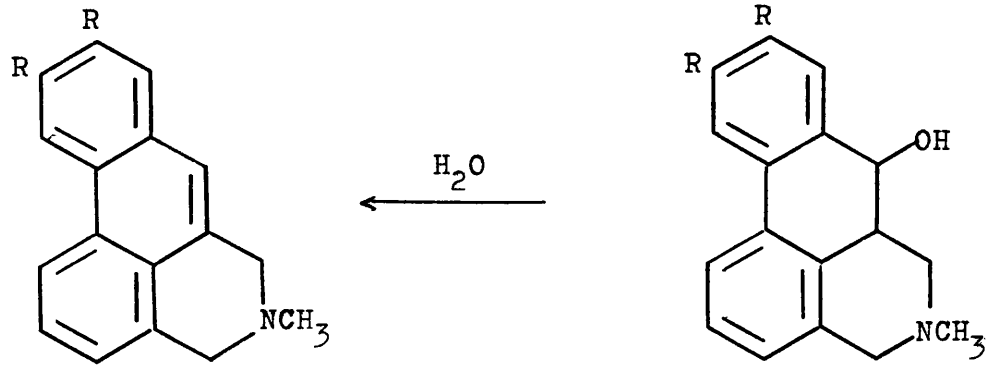
(64)a R = H

(64)b R = OCH_3

(65)a R = H

(65)b R = OCH_3





(67)a R = H

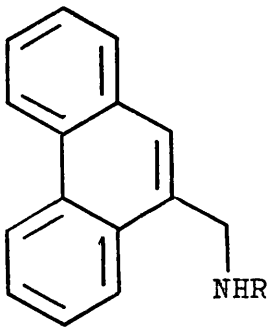
(67)b R = OCH_3

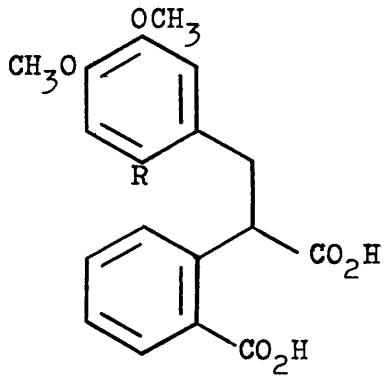
(66)a R = H

(66)b R = OCH_3

An attempt to extend this synthesis to the compound (67b) was abandoned due to the very poor yield in the reduction of (64b) to (65b). When 2-methyl-1,2-dihydroisoquinoline was treated with 6-nitropiperonyl chloride a crystalline product could not be obtained.

Attempts[28] to cyclise (68a) under the conditions of the Bischler-Napieralski reaction, and (68b) in a Pictet-Spengler reaction were unsuccessful, presumably due to the fact that the phenanthrene nucleus was not activated.





(68)a R = CHO

(68)b R = H

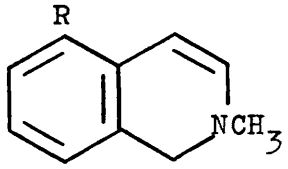
(69)a R = NO_2

(69)b R = NH_2

Attention was next turned to Pschorr's original method and reactions of homophthalic acid with a number of aldehydes was examined. Condensation with 6-nitroveratraldehyde afforded the required product (69a) in moderate yield, whereas with 6-nitropiperonal the reaction failed. When homophthalic anhydride was substituted for the acid yields of (69a) were very poor. Reduction of (69a) to (69b) occurred in only 26% yield and Pschorr cyclisation afforded (61b) in 29% yield. Treatment of (61b)

with methylamine afforded (58b) in 1% overall yield from homophthalic acid.

The obvious modification of Pschorr's synthesis namely cyclisation of a 4-benzyl-5-aminoisoquinoline was investigated. However difficulty was encountered in the synthesis of the required starting material. An attempt to condense 2-methyl-5-nitro-1,2-dihydroisoquinoline (70a) with benzaldehyde in 6M HCl/ethanol was unsuccessful. It was thought that the failure of this reaction was due to protonation occurring at oxygen to give (71), rather that at C_4. Therefore in a subsequent experiment 5-benzoylamino-1,2-dihydroisoquinoline (70b) was reacted with

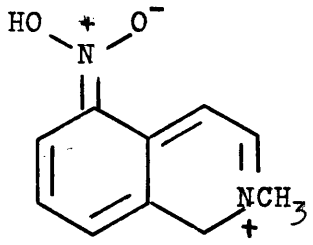


(70)a R = NO_2

(70)b R = NHCOPh

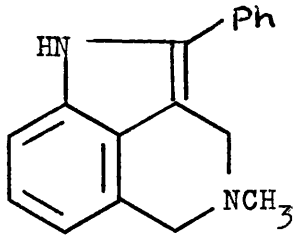
(70)c R = $NHCOCH_3$

(70)d R = $NHCO_2Et$

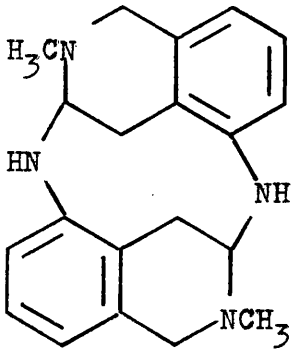


(71)

benzaldehyde in acid solution. On this occas ion the only products were two bases which were assigned the structures (72) and (73) on the basis of; the absence of amide carbonyl absorption in the IR, the mass spectral fragmentations and the fact that the same products were formed when the 5-benzoyl amino compound was replaced by the acetamido compound (70c) or the carbamate (70d).

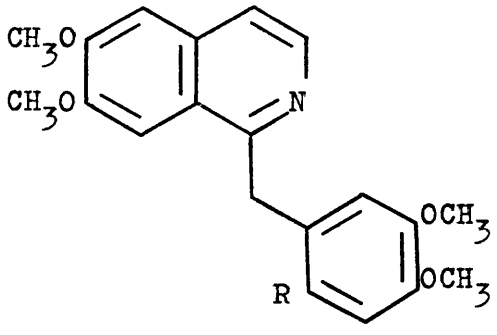


(72)

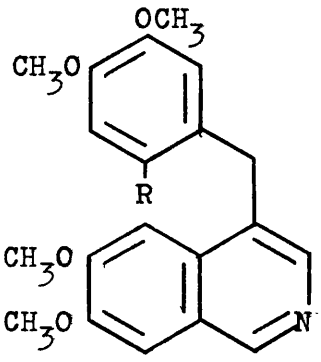


(73)

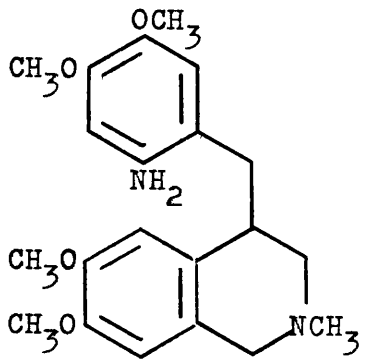
By analogy with the nitration of papaverine (74R,=H) to give 6-nitropapaverine (74,R=NO_2),[29] it was found that nitration of the isomeric 4-benzyl isoquinoline (75,R=H) gave (75,R=NO_2) in 88% yield. N-methylation followed by reduction gave (76) which was subjected to a Pschorr reaction to yield the dibenz [de,g] isoquinoline (77) in very poor yield.



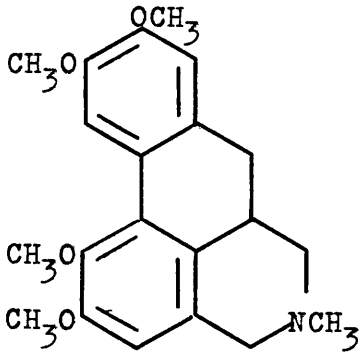
(74)



(75)

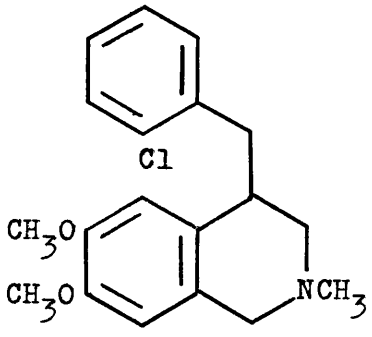


(76)

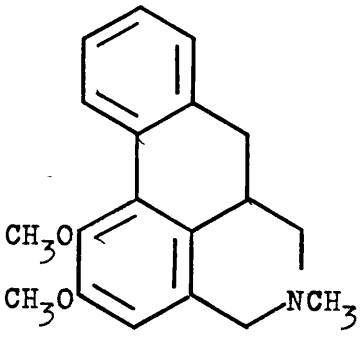


(77)

More recently attempts to synthesise the dibenz [de,g] isoquinoline (79) by treatment of 2-methyl-4-(6-chlorobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (78) with a variety of reagents including $PdCl_2$, $Pd(OAc)_2$ sodamide in benzene and sodium in liquid ammonia have proved unsuccessful[30]. The starting material was returned unchanged in each case.



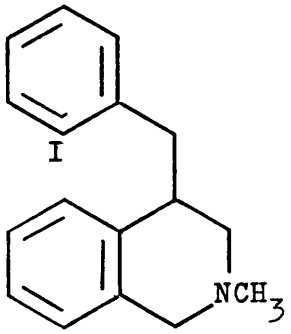
(78)



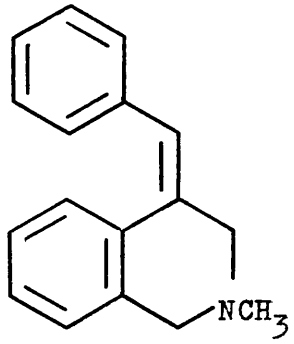
(79)

Other possible syntheses of the dibenz [de,g] isoquinoline system might include photocyclisation of 4-(6-iodobenzyl) tetrahydroisoquinolines (80) or of 4-benzylidene tetrahydro-

isoquinolines (81) by analogy with similar syntheses of the aporphine system[31-33].



(80)



(81)

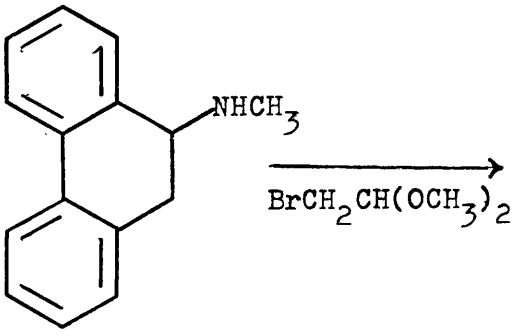
Finally, and again by analogy with similar syntheses of aporphines, intramolecular oxidative aryl-aryl coupling of 4-benzyltetrahydroisoquinolines might be expected to provide a useful synthetic approach to the dibenz [de,g] isoquinoline system.

The first part of the discussion and experimental sections of this chapter describes a successful synthesis of dibenzy [de,g] isoquinoline derivatives by intramolecular oxidative coupling of 4-benzyltetrahydroisoquinolines using vanadium oxytrifluoride. Also described are a number of attempts to isolate a postulated intermediate in this reaction. The isolation in the course of this work of a potential precursor, led the author to attempt the synthesis of a 4-benzylidine tetrahydroisoquinoline of the type (81) required for a photochemical synthesis of dibenz [de,g] isoquinoline derivatives.

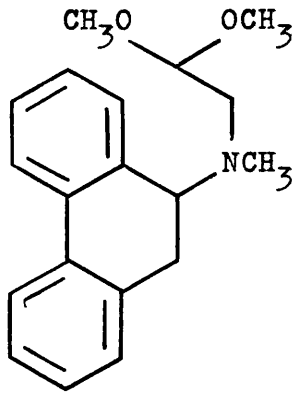
9-Amino-phenanthrenes

The second part of this chapter describes a successful

synthesis of a 9-amino-phenanthrene derivative by oxidative coupling of a 1,2-diarylethylamine derivative. Such phenanthrenes are important synthetic intermediates and could provide a route to the 4-hydroxy aporphines (85) as shown (83)→ (85). The final cyclisation would require activation in the potential A ring of the aporphine, preferably <u>para</u> to the point of ring closure.

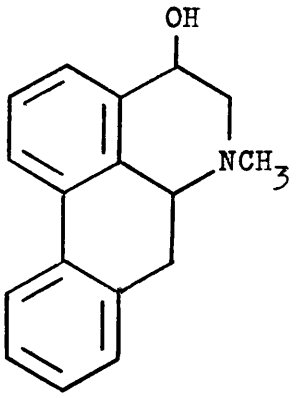


(83)



(84)

mild acid

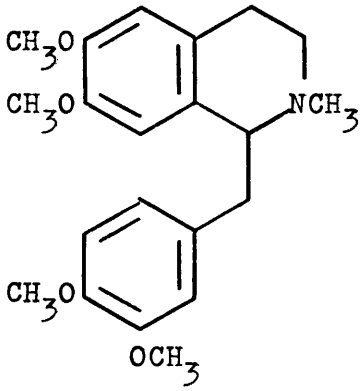


(85)

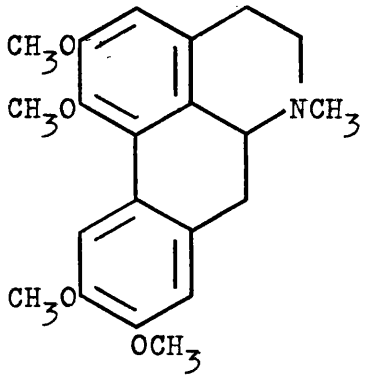
DISCUSSION

Synthesis of dibenz [de,g] isoquinoline derivatives

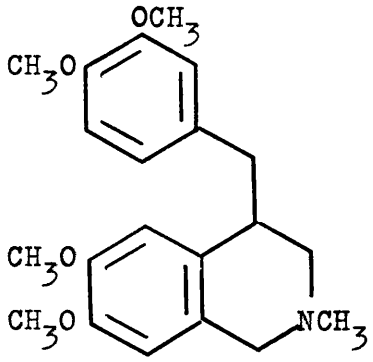
Kupchan reported[11] that treatment of (±)-laudanosine (86) in trifluoroacetic acid, fluorosulphonic acid and dichloromethane at -30°, with a solution of VOF_3 in trifluoroacetic acid afforded (±) glaucine (87) in 43% yield. It was therefore reasoned that similar treatment of the isomeric 4-benzyltetrahydroisoquinoline (88) might yield the dibenz [de,g] isoquinoline derivative (89).



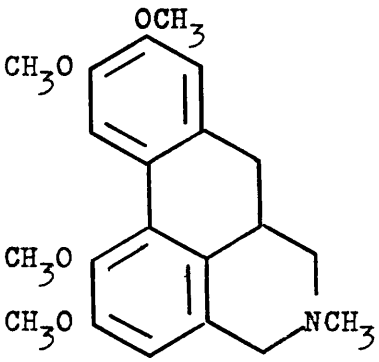
(86)



(87)

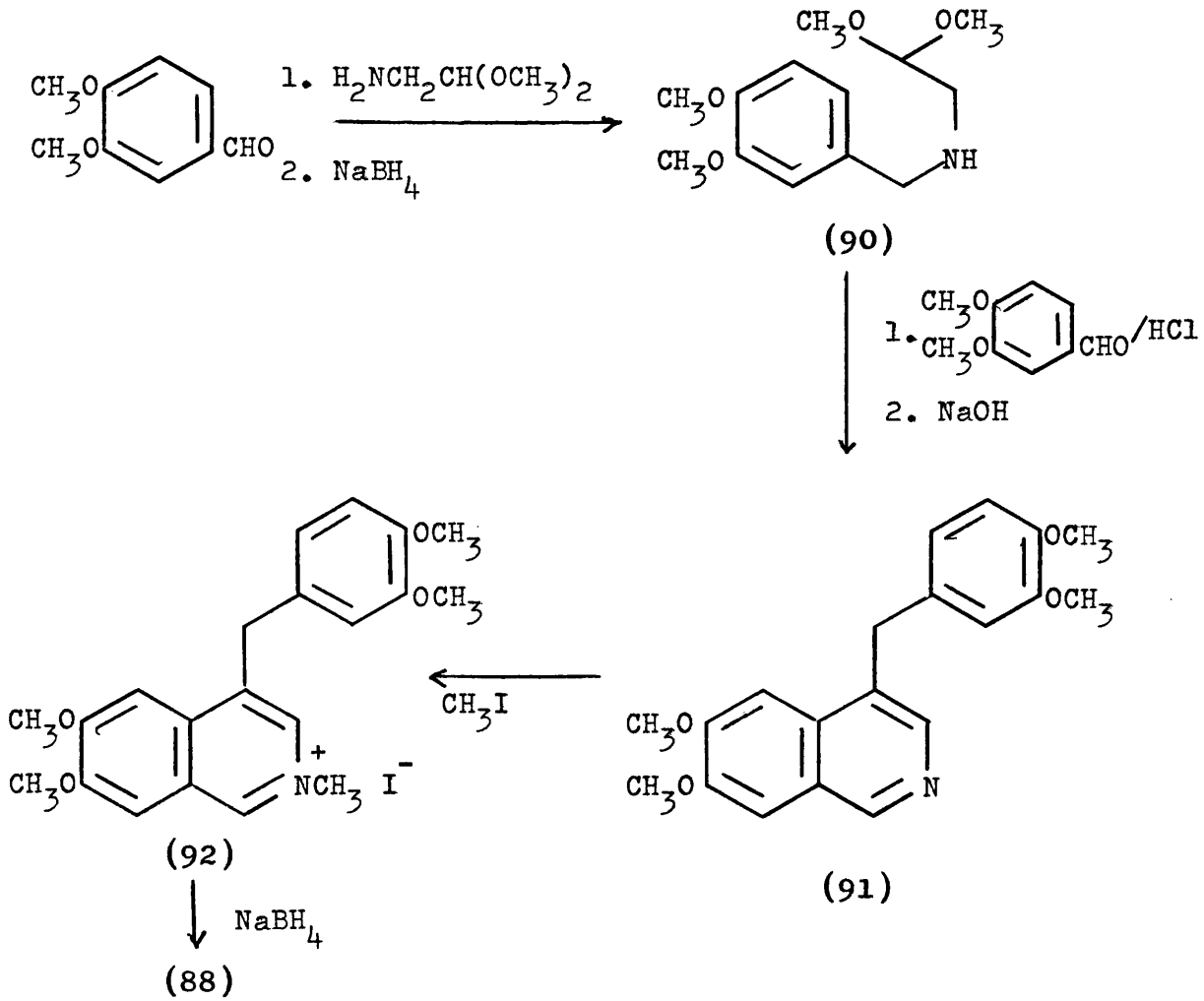


(88)



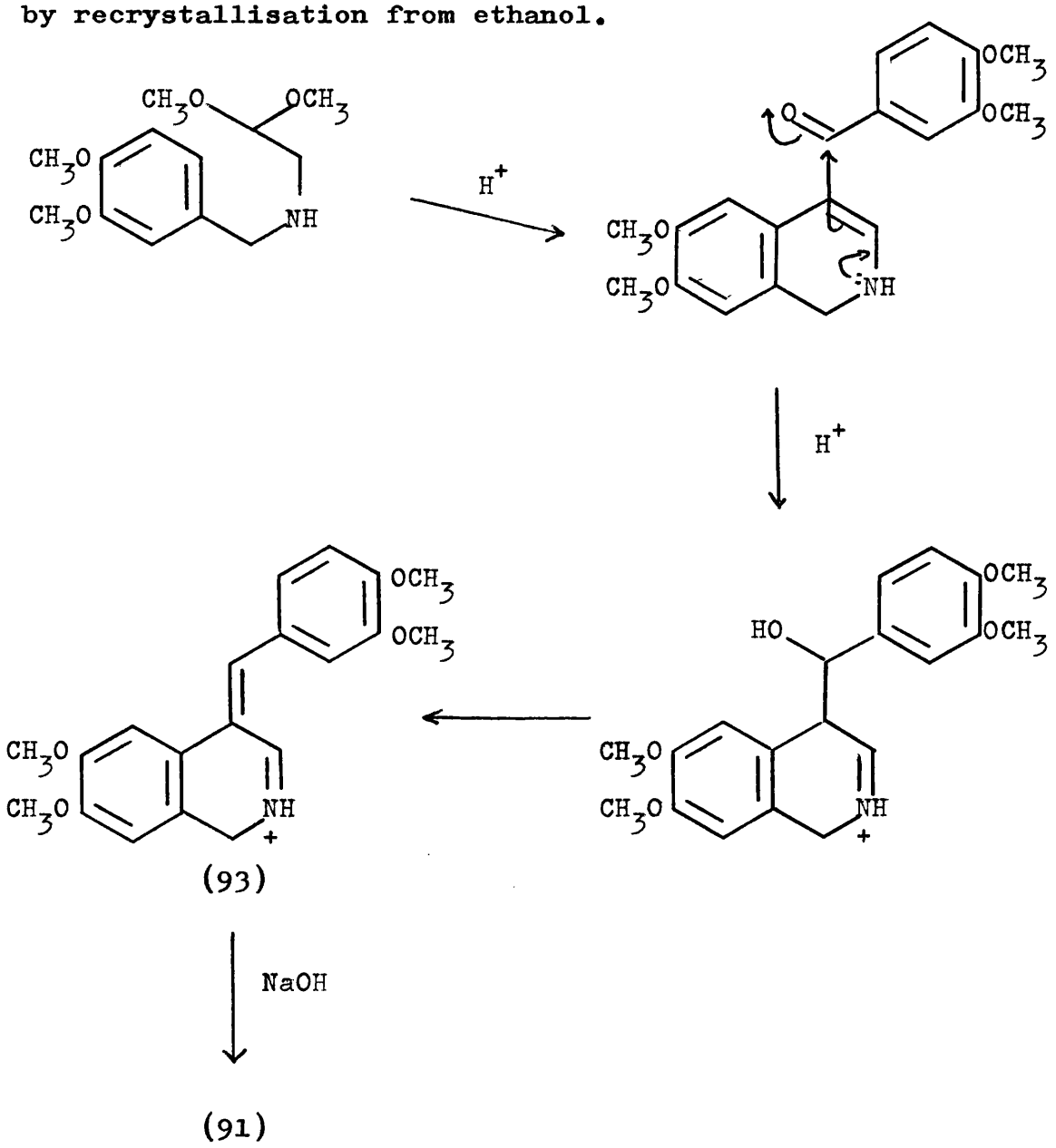
(89)

The required 4-benzyltetrahydroisoquinoline (88) was prepared by the route outlined in scheme 7. Veratraldehyde and aminoacetaldehyde dimethyl acetal were condensed in ethanol and the resultant imine was without isolation, reduced with sodium borohydride to afford the acetal (90). Condensation with a slight excess of veratraldehyde in 6M ethanolic hydrochloric acid at reflux afforded upon basification, the 4-benzylisoquinoline (91)[24]. A mechanism for the latter condensation has been proposed[34] (scheme 8). The reaction was characterised by the development of a deep red colouration due to the intermediate 4-benzylidine compound (93)[35], which was without isolation, isomerised to the fully aromatic isoquinoline (91) by refluxing with base. The compound



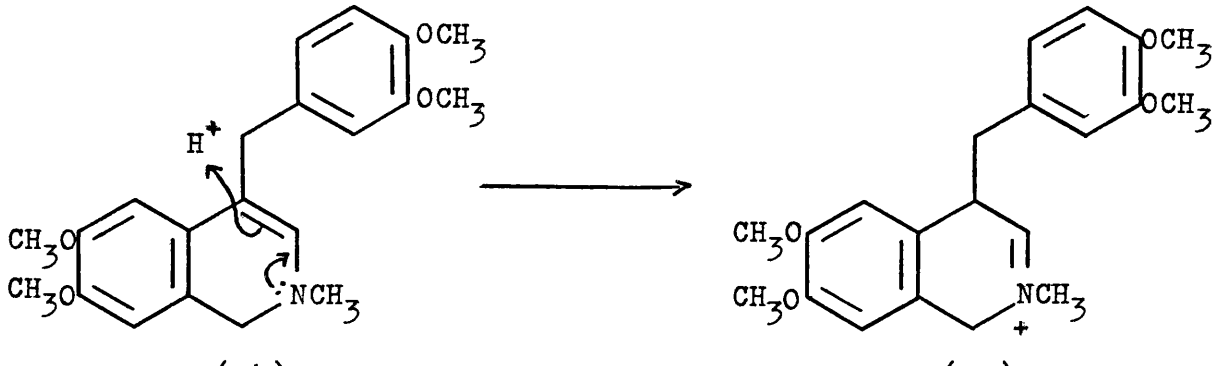
Scheme 7

(91) was obtained as a brown gum which could not be persuaded to crystallise from a number of solvents. However, treatment of an acetone solution of the crude product with methyl iodide afforded a fairly good yield of the crystalline methiodide (92) which could be purified by recrystallisation from ethanol.



Scheme 8

Numerous attempts to reduce the methiodide (92) with sodium borohydride resulted in only partial success, giving inseparable mixtures of the required tetrahydroisoquinoline (88) and other products. It is generally accepted that metal hydride reduction of compounds of this type occur in two stages. (Scheme 9). Firstly rapid reduction of the 1,2 bond takes place, to give the 1,2-dihydroisoquinoline (94). Protonation at the β carbon of the enamine system then gives the immonium ion (95) which is attacked by another hydride ion. Thus for the second stage of reduction to occur a source of protons is required. Furthermore, the ease with which this second stage occurs depends on the basicity of the enamine, which is dictated by the nature of the substituents on the α and β carbon atoms. In compound (94), two effects are operating to decrease the basicity of the β position of the enamine system, namely:
a) hyperconjugative stabilisation of the 3,4-double bond by the CH_2 protons of the 4-benzyl group and
b) the mesomeric effect of the 6 and 7 methoxy substituents which is opposing the polarisation required for β protonation.

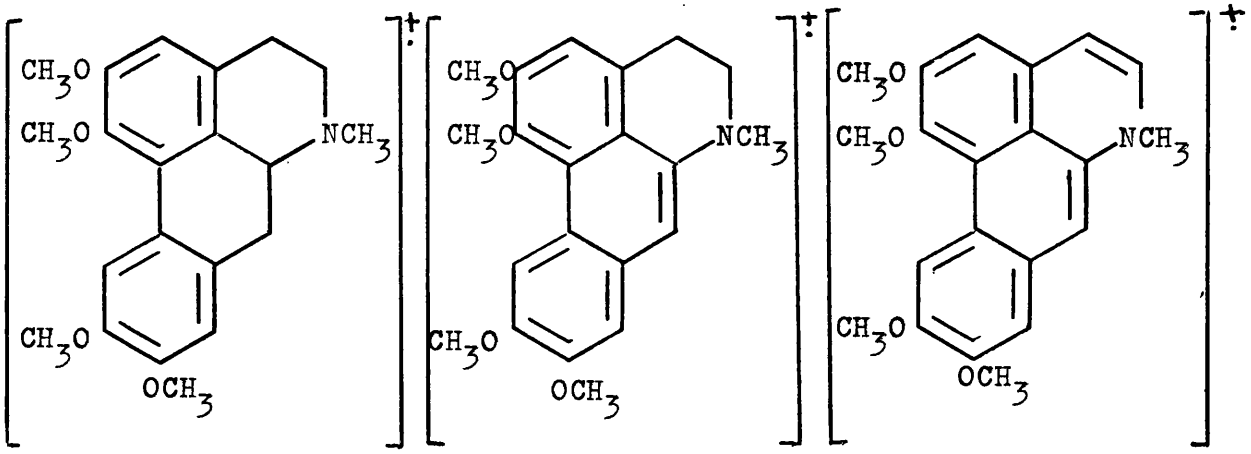


(94) (95)

Scheme 9

The reduction was eventually achieved in excellent yield using a large excess of sodium borohydride in 1:1 aqueous ethanol at 60°.

The paper by Kupchan describing the oxidation of (±) laudanosine to (±) glaucine[11] did not give details of the experimental procedure. Therefore in order to determine the conditions for intramolecular oxidative coupling, initial oxidations with VOF_3 were carried out on (±)-laudanosine, prepared by sodium borohydride reduction of papaverine methiodide. Several attempts to duplicate Kupchan's results met with failure. Vanadium oxytrifluoride was found to be relatively insoluble in trifluoracetic acid, however, 60:40 trifluoroacetic acid - ethylacetate was found[36] to be a suitable solvent. Eventually, treatment of a solution of laudanosine in 1:1 trifluoroacetic acid - dichloromethane with an excess of VOF_3 in 60:40 trifluoroacetic acid - ethylacetate at -30° afforded after column chromatography of the crude product, a 30% yield of glaucine as a brown gum. The product could not be persuaded to crystallise as either the free base or as the hydrochloride and, although the spectral data was in agreement with that reported for glaucine[3,37], both the nmr and the mass spectrum indicated the presence of impurity not detected by thin layer chromatography. The UV spectrum showed absorption maxima at 244, 284 and 301 and the nmr spectrum indicated the presence of three aromatic protons resonating as singlets. The mass spectrum showed fairly strong peaks at m/e 355, 353 and 351 consistent with the expected ions (96), (97) and (98).



(96) (97) (98)

Treatment of the 4-benzyltetrahydroisoquinoline (88) with VOF_3 under the same conditions failed to yield the glaucine isomer (89).

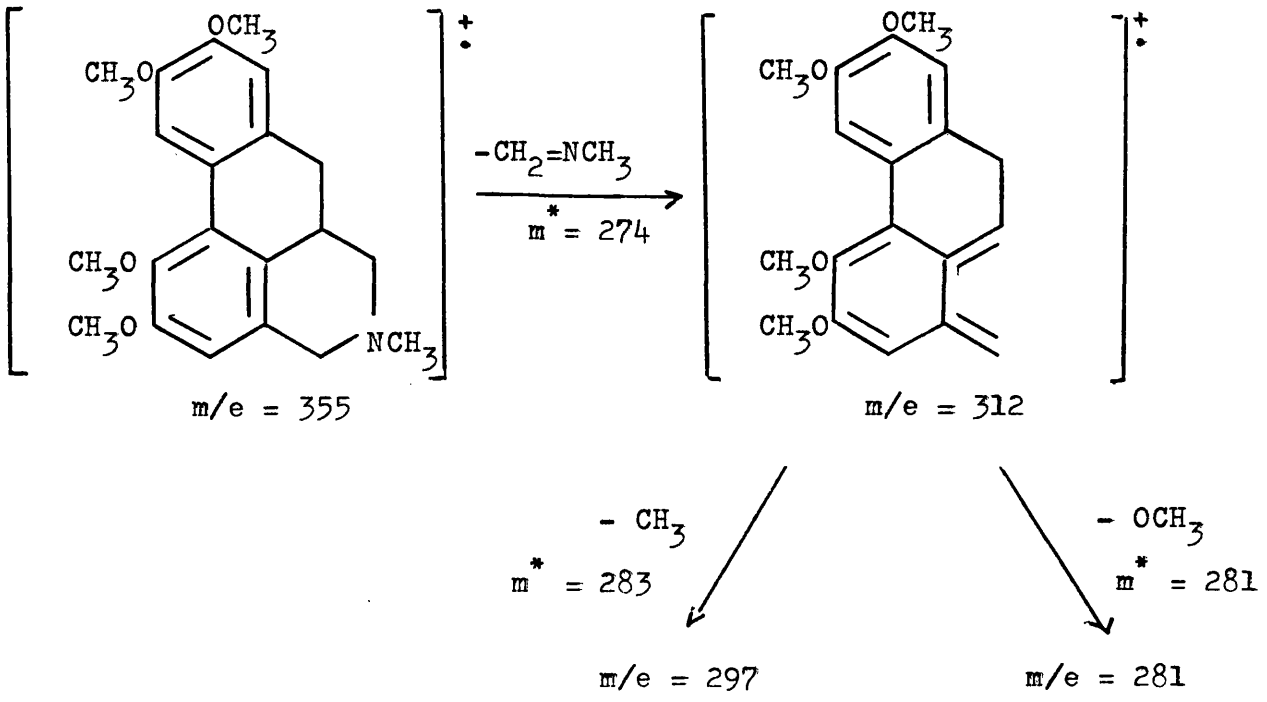
In later publications[15,16] Kupchan reported more details of a successful experimental procedure. In particular the use of trifluoroacetic anhydride in the solvent mixtures to absorb traces of moisture and the use of a smaller excess of VOF_3 in these later experiments was significant. A further attempt to effect the desired coupling of (88) under these conditions using carefully dried solvents, afforded after five hours, a mixture of two products, which were separated by column chromatography.

The spectral characteristics of the major component (38%) were consistent with those predicted for the structure (89). The UV spectrum was as expected, very similar to that of glaucine, showing absorption maxima at 230, 282 and 303 nm.

The use of nmr in structure elucidation of aporphines revolves mainly around the fact that methoxyl groups at

C-1 or C-11 appear at higher field (3.72-3.4 δ) than other methoxyl groups (3.9-3.72 δ), while a hydrogen at C-11 resonates at lower field (8.1-7.57 δ) than the other aromatic protons (7.0-6.38 δ).[3] By analogy it was expected that the C_1 methoxyl of (89) would appear at higher field than the other three methoxyls and that the hydrogen at C-11 would appear at lower field than the other two aromatic protons. This was born out in practice. The nmr spectrum of (89) showed three aromatic protons resonating as singlets, with one resonating at lower field (8.12 δ) than the other two (6.73 and 6.53 δ). The spectrum also showed one methoxyl group resonating at higher field (3.65 δ) than the other three (3.89-3.84 δ).

The mass spectrum could be rationalized in terms of the fragmentations shown in scheme 10. Although the free base could not be persuaded to crystallise, an analytically pure crystalline hydrochloride was obtained by treating a concentrated acetone solution of the product with concentrated hydrochloric acid.

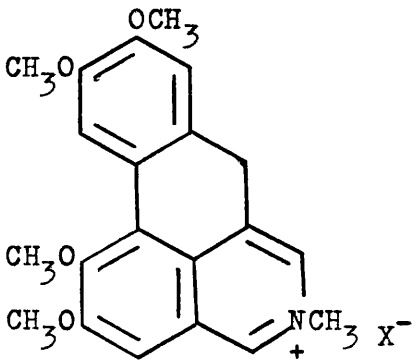


Scheme 10

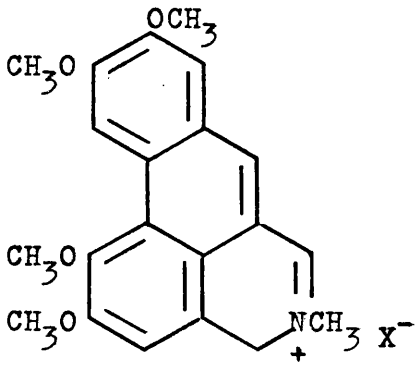
The minor component (10%) was an orange solid showing greater solubility in water than in benzene. The UV spectrum was poorly resolved, although maxima were visible at 240, 273 and 450 nm. The mass spectrum showed a molecular ion at m/e 351 supported by the low eV trace and the isotopic abundance of the $(M^+ + 1)$ peak. The base peak was located at m/e 320 $(M^+ - 31)$, presumably arising by loss of methoxyl from the molecular ion. That the required cyclisation had occurred was indicated by the high relative abundance of the molecular ion. If cyclisation had not occurred, some fragmentation involving loss of the 4-benzyl function would have been expected. The nmr spectrum of the product showed one proton singlets at 9.68, 8.87, 7.33, 7.26 and 6.51, with other absorptions occurring between 4.2 and 3.4 ppm. Attempts to crystallise the product

were unsuccessful.

The structures (99) or (100) were proposed on the basis of this evidence. Both might be expected to lose HX in the mass spectrometer to give a molecular ion at 351 and both could arise by over oxidation of (89).



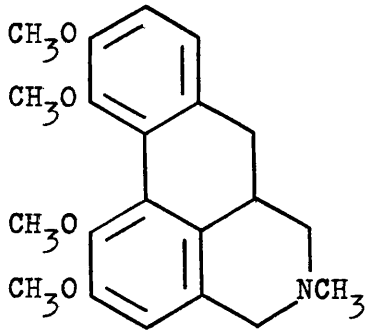
(99)



(100)

Structures such as (99) and (100) would be expected to be susceptible to reduction with sodium borohydride. However, treatment of this minor component with sodium borohydride in 1:1 aqueous ethanol at 60° resulted in no change in the UV, nmr or mass spectra. Hence there is some doubt as to the correctness of this structural assignment.

None of the alternative ortho-ortho coupled product (101) was detected in the reaction mixture. The nmr spectrum of this alternative product would exhibit ortho coupling between the two adjacent aromatic protons.

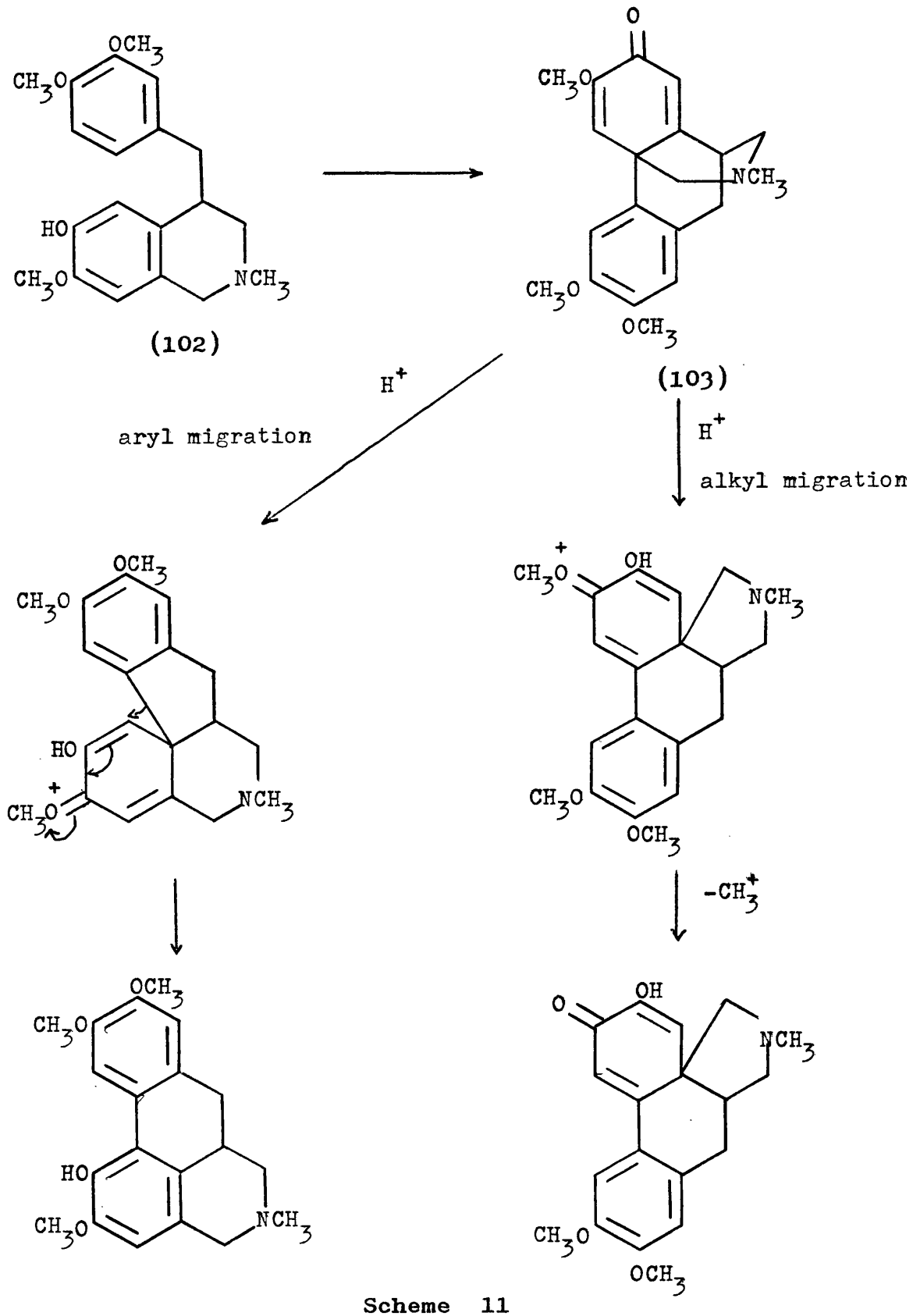


(101)

At this stage attention was turned to the coupling of monophenolic substrates as, in the case of the 1-benzyl and 1-phenethylisoquinolines, yields of the coupled products were generally better when phenolic substrates rather than non phenolic substrates were used.

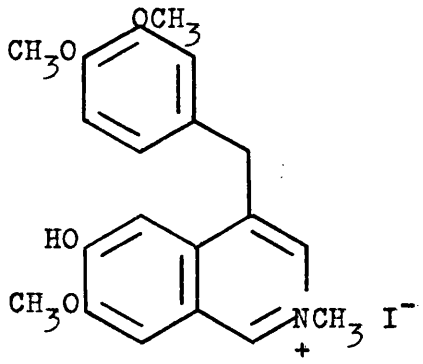
By analogy with the proposed intermediacy of morphinandienones in the chemical and electrooxidative coupling of 1-benzyltetrahydroisoquinolines[14], it was postulated that oxidation of the 4-benzyltetrahydroisoquinolines might initially involve the formation of "isomorphinandienone" intermediates of the type (103). Such intermediates could undergo acid catalysed rearrangements analogous to those which morphinandienones undergo (scheme 11). However, in the case of the "isomorphinandienone" system, the availability of the nitrogen lone pair would not be expected to play a major role in determining which mode of rearrangement was favoured. Therefore, the substrate chosen for examination was the 6-hydroxyisoquinoline (102),

as the position of the hydroxy group in this molecule would favour formation of the postulated "isomorphinandienone" intermediate, initial coupling being expected to occur <u>para</u> to the hydroxy group (scheme 11).

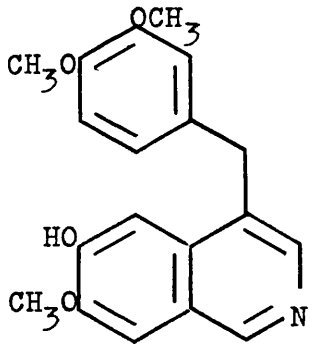


Scheme 11

The phenolic 4-benzyltetrahydroisoquinoline (102) was prepared by an analogous route to that used in the preparation of the tetramethoxy analogue (scheme 7). However, the yield of the isoquinoline methiodide (104) was poor and despite numerous attempts, could not be improved by alterations in the work up procedure of the Bobbit reaction. The problem was in part caused by the insolubility of the fully aromatic isoquinoline (105) in the normal solvents used for methiodide formation. This may have been due to the ability of (105) to exist as a zwitterion. Although a number of solvents were tried, none showed any advantage over acetone.



(104)



(105)

Reduction of the methiodide (104) under the conditions previously described proceeded in excellent yield. The resultant tetrahydroisoquinoline (102) was subjected to oxidation with VOF_3 for five hours under the same conditions as used for the tetramethoxy compound. Column chromatography of the crude product afforded two components in yields of 70% and 12% respectively.

The spectral and analytical data of the major product, which crystallised from ethanol as large colourless prisms, were consistent with the ortho-para coupled structure (106). The minor product crystallised from chloroform as large colourless hexagonal prisms which turned opaque orange upon vacuum drying at room temperature. This product was assigned the structure (107) on the basis of the following evidence:

The UV spectrum exhibited absorption maxima at 235, 277, 321, 330 and 447 nm and, apart from a slight increase in absorption intensities, showed no change on addition of base. The infrared spectrum was devoid of carbonyl absorption, thus precluding a dienone structure. Nmr spectroscopy indicated four aromatic protons resonating as singlets at 8.8, 7.13, 6.5 and 6.21 and three magnetically non equivalent methoxyl groups resonating as singlets. A three proton singlet at 3.14 was attributed to the N-methyl group, thus indicating the nitrogen to be quaternary. The base peak in the mass spectrum was located at m/e 339, and other strong peaks were located at m/e 341, 340, 338, 324, 298, 283 and 267. The presence of metastable ions at m/e 260.4, 268.75 and 239.2 confirmed the following fragmentations:

i) $341 \xrightarrow{-43} 298$ probably retro Diels-Alder loss of $CH_2{=}NCH_3$;

ii) $298 \xrightarrow{-15} 283$ corresponding to loss of methyl group;

iii) $298 \xrightarrow{-31} 267$ corresponding to loss of methoxyl.

In addition a metastable at m/e 309.7 confirmed the fragmentation

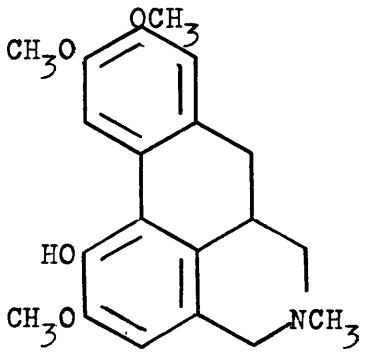
339 $\xrightarrow{-15}$ 324, presumably arising by loss of a methyl group. The base peak at 339 is probably due to (108) arising by loss of HX from (107). A similar loss of HX might be responsible for the unusual melting characteristics of this product. The product softened to a red gum over the range 96-100°, but a crystalline form was reassumed over the range 130-140°. This latter solid melted at 145°.

It was thought that this minor product could have arisen by over oxidation of (106). In order to confirm this a small sample of (106) was subjected to further oxidation with VOF_3, whereupon thin layer chromatography and UV spectroscopy indicated complete conversion to the minor product. Further evidence to support the proposed structure (107), was provided by treatment of a small sample of the minor product with sodium borohydride in 1:1 aqueous - ethanol, whereupon complete conversion to (106) was confirmed by thin layer chromatography, UV and mass spectral data.

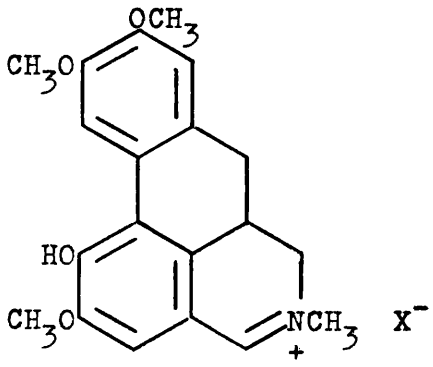
In order to account for the strong ion at m/e 341 and the associated fragment ions at m/e 298, 383 and 267 in the mass spectrum, it is necessary to postulate that hydrogen capture to give (106) occurs in the mass spectrometer. Initial suggestions that these ions might be due to contamination with (106) were discounted on the basis that one could expect such a level of contamination to be detected by nmr and thin layer chromatography.

One observation that could not be accounted for on the basis of structure (107), was the fact that only one

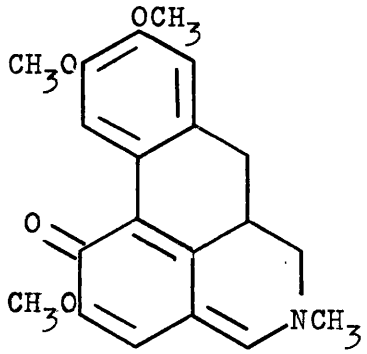
proton resonated at lower field than 8.0 ppm in the nmr spectrum. If the singlet at 8.8 ppm is assigned to the C-4 proton, one might expect, on the basis of previous observations, a second signal due to the proton on C-11 to appear between 8.0 and 9.0 ppm.



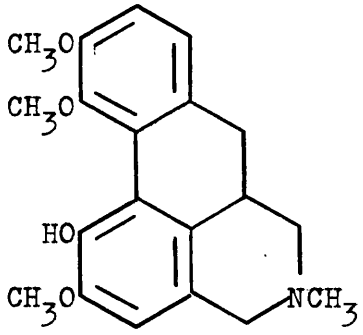
(106)



(107)



(108)



(109)

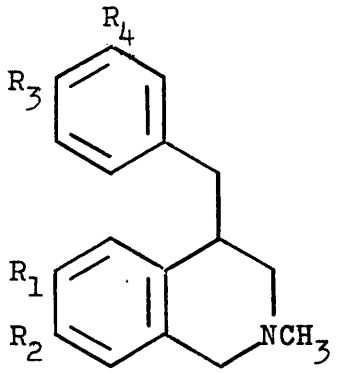
Once again none of the alternative ortho-ortho coupled product (109) was detected in the reaction mixture.

The fact that no products of over oxidation have been reported to occur in the oxidation of 1-benzylisoquinolines may be due to oxidation of the C(1)-N bond of the isoquinoline moiety of that system being less favoured due to the presence of the C-1 substituent.

In an attempt to isolate the postulated "isomorphinandienone" intermediate (103), the oxidation of (102) was repeated, but the reaction worked up after only 10 minutes. In this way it was hoped to stop the reaction before the intermediate (103) had time to rearrange. However the same mixture of products in approximately the same proportions as isolated previously was obtained.

In two further attempts to isolate (103), the oxidation of (102) was repeated in the absence of added acid, in order to minimise the possibility of acid catalysed rearrangement of (103). No acid was used in the work up and all chromatography was carried out on basic alumina. However under these conditions no reaction had occurred after ten minutes or again after five hours, indicating that acid must be present in order for any reaction to take place.

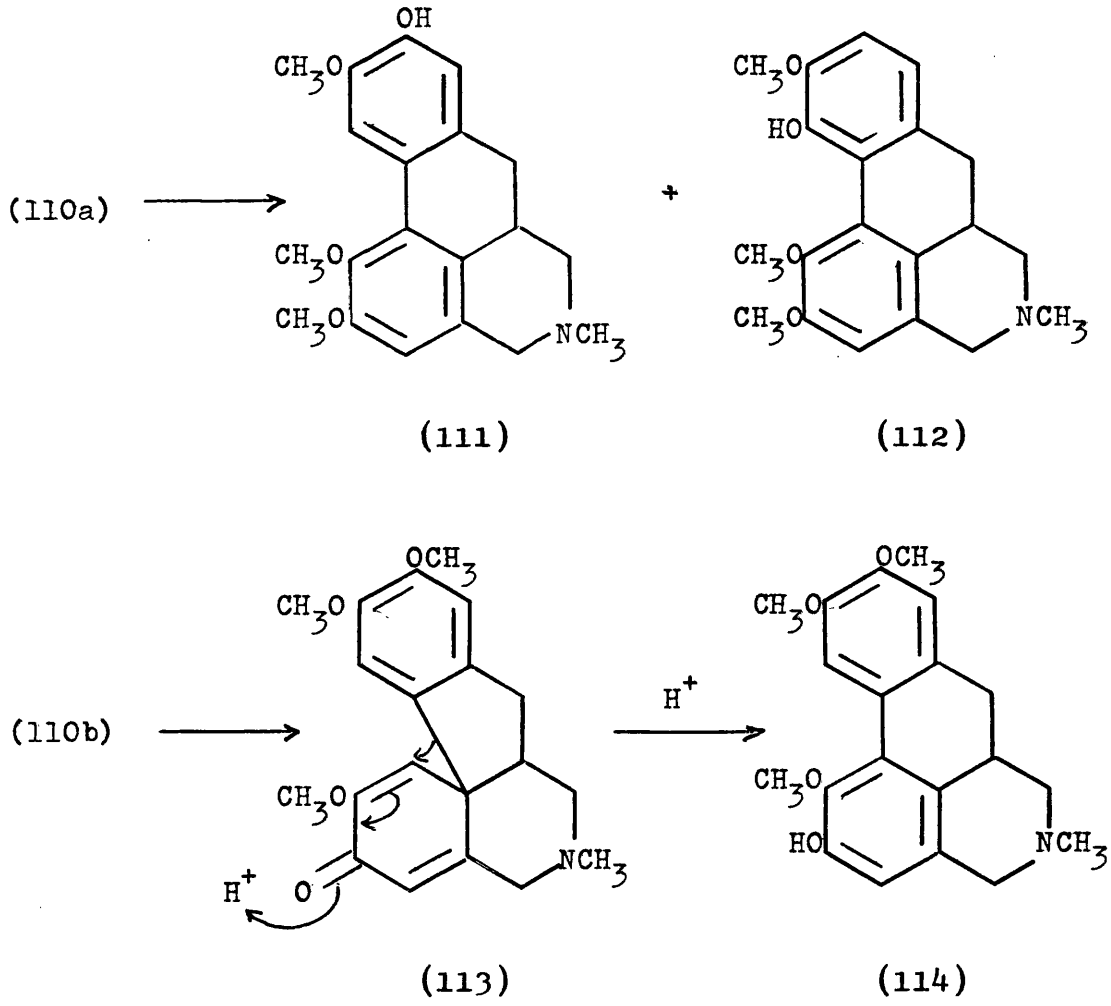
The author decided to examine the effect of varying the position of the phenolic hydroxyl group on the course of the oxidative coupling reaction. Accordingly a series of monophenolic 4-benzyl-tetrahydroisoquinolines (110a-d) were prepared by the standard method (scheme 7). As in the preparation of (102), the yields of the corresponding 4-benzylisoquinoline methiodides were poor and could not be improved by changes in either the conditions or work up of the Bobbit condensation. However, when sufficient quantities of the methiodides had been obtained, reduction to the tetrahydro compounds (110a-d) proceeded in excellent yield.



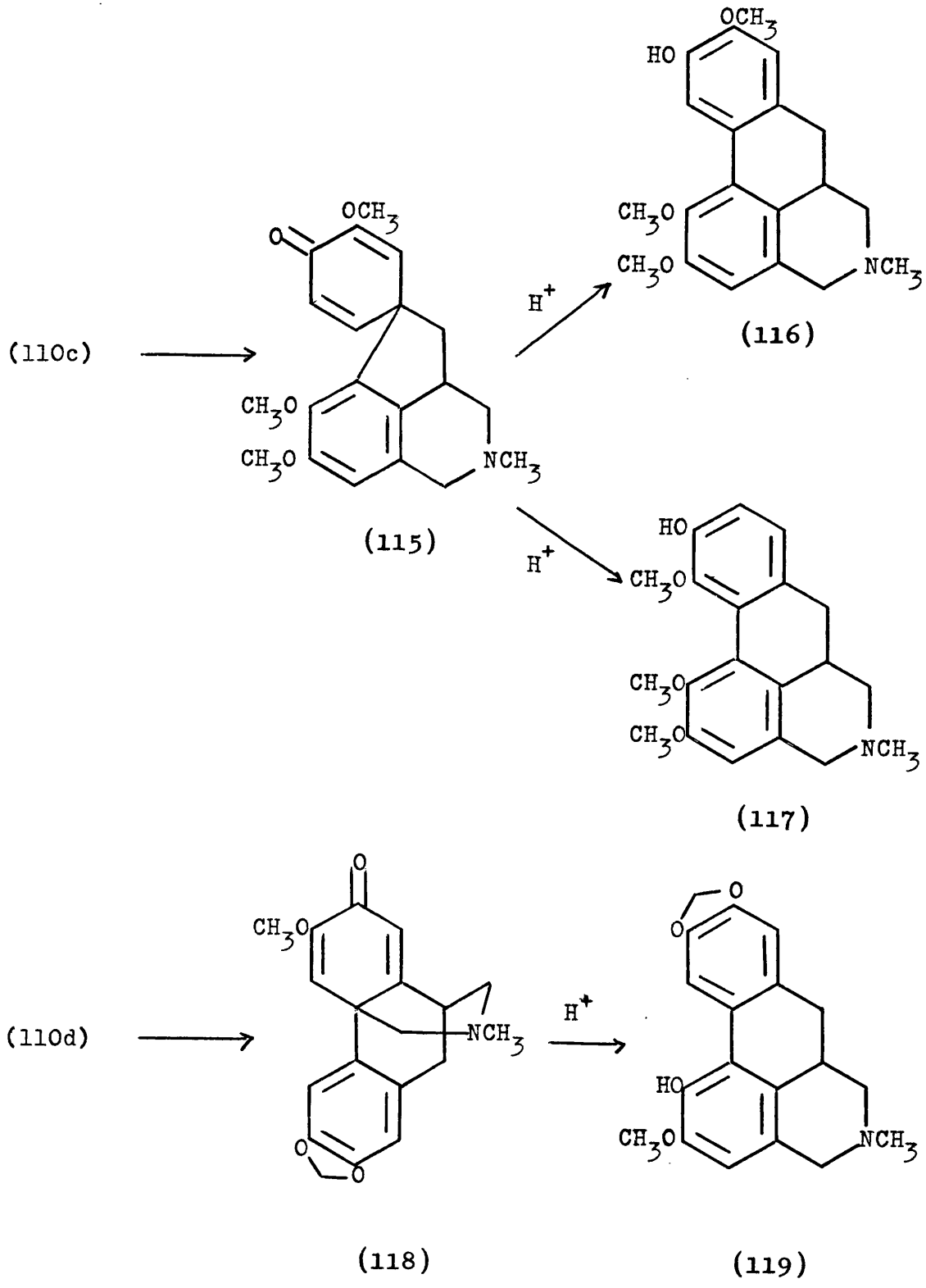
	R_1	R_2	R_3	R_4
(110a)	OCH_3	OCH_3	OCH_3	OH
(110b)	OCH_3	OH	OCH_3	OCH_3
(110c)	OCH_3	OCH_3	OH	OCH_3
(110d)	OH	OCH_3	O - CH_2 - O	

The expected products of the oxidation of these substrates are shown in scheme 12. The position of the hydroxyl group in (110a) would favour direct para coupling to give the 1,2,9,10-substituted derivative (111) as the major product. However, some coupling ortho to the hydroxyl to give the 1,2,10,11-substituted derivative (112) might be expected. In the case of compound (110b), initial coupling para to the hydroxyl function would yield the dienone (113), which could undergo acid catalysed rearrangement to the 1,2,9,10-substituted derivative (114). Coupling para to the hydroxy function in (110c) would afford the dienone (115). In this case two modes of acid

catalysed rearrangement are possible; one giving rise to the 1,2,9,10-substituted derivative (116) and the other giving rise to the 1,2,10,11-substituted derivative (117). The mesomeric effect of the methoxyl would be expected to favour the former mode. Interest in the compound (110d) stemmed from a desire to determine whether the method could be used for the synthesis of the compounds containing methylenedioxy functions.



Schema 12



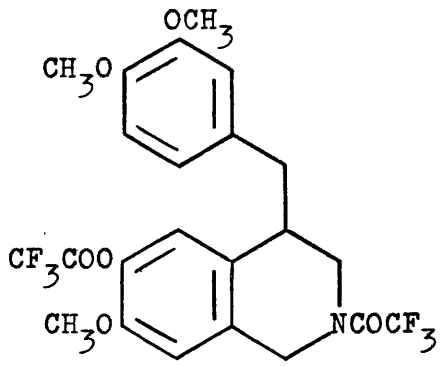
Scheme 12 (cont.)

Treatment of the substrates (110a-d) with VOF_3, for five hours under the conditions used previously, resulted in each case, in the formation of black tarry multicomponent mixtures from which no identifiable products could be isolated. The U.V. spectra of these crude products showed little or no evidence of biphenyl coupling (λ max 300 nm). The reactions were repeated with a reaction time of 10 minutes, but similar results were obtained and none of the expected products (111) to (119) could be isolated.

The effect of nitrogen lone pair availability on the course of oxidative coupling of 4-benzylisoquinolines

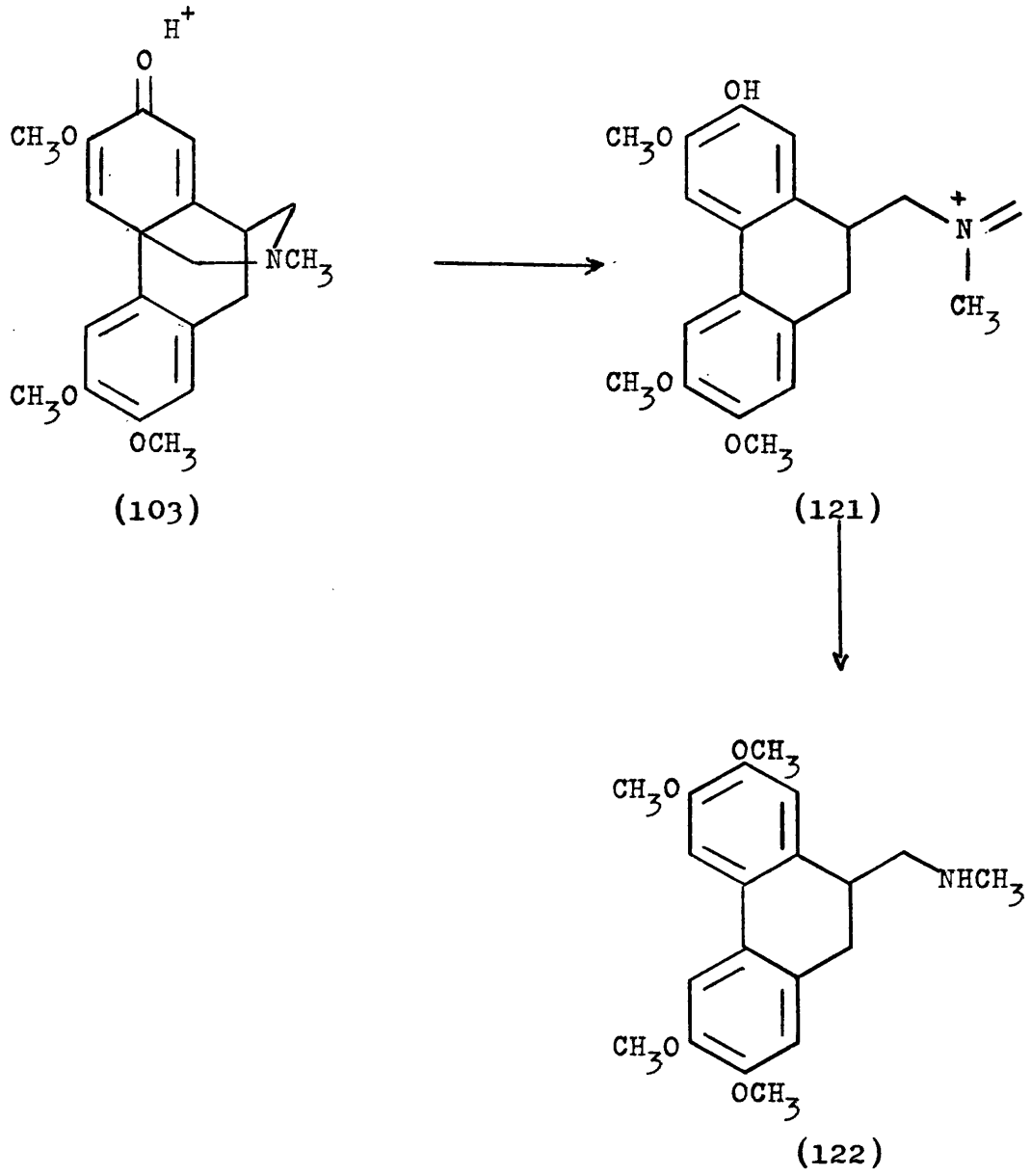
The availability of the nitrogen lone pair electrons had been found to play a significant role in determining the nature of the products obtained in the oxidation of 1-benzyl and 1-phenethylisoquinolines with VOF_3. The presence of an electron withdrawing group such as formyl or trifluoracetyl on the nitrogen atom was found to alter the favoured mode of rearrangement of the postulated morphinandienone intermediates formed in the oxidation of the 1-benzyl compounds.

In order to establish whether nitrogen lone pair availability played a similar role in determining the nature of the products in the oxidation of 4-benzyl-isoquinolines, the author decided to examine the oxidation of the O,N-bistrifluoracetyl derivative (120).



(120)

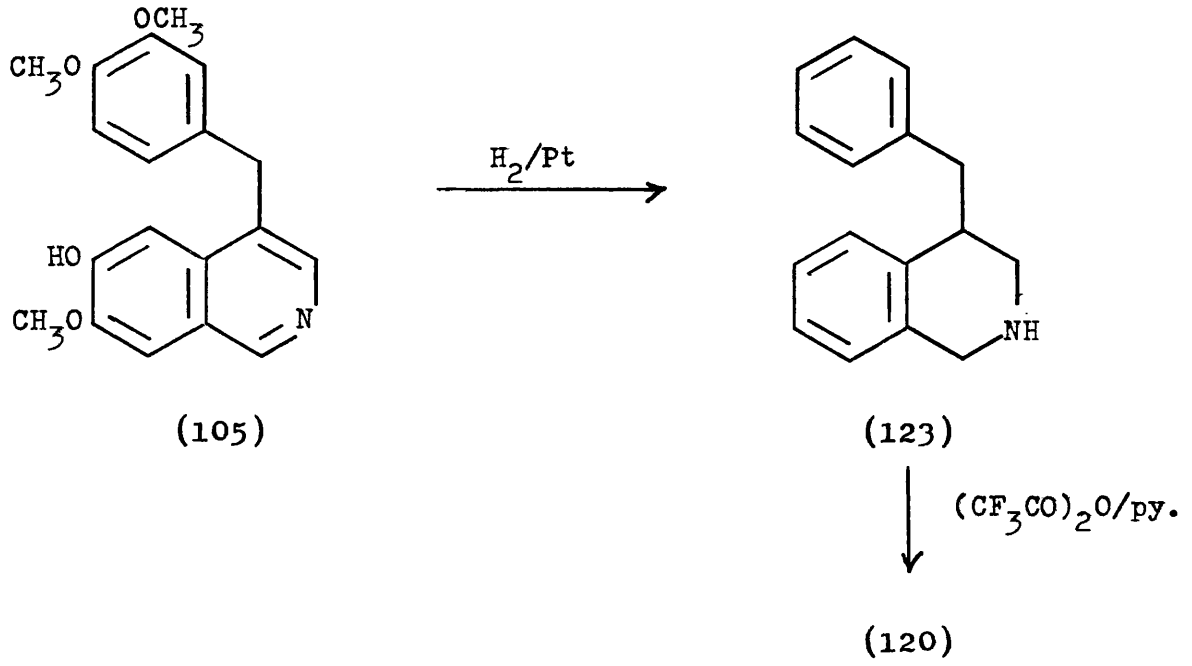
An alternative mode of reaction of the postulated "isomorphinandienone" intermediate (103), might be that shown in scheme 13, involving ring opening to (121) followed by rapid hydrolysis to (122). Hence such intermediates might be too unstable to isolate. However, the possibility of such a ring opening reaction would be greatly reduced by the presence of an electron withdrawing function on the nitrogen atom and it was hoped that oxidation of (120) would afford an isolable "isomorphinandienone".



(103) (121) (122)

Scheme 13

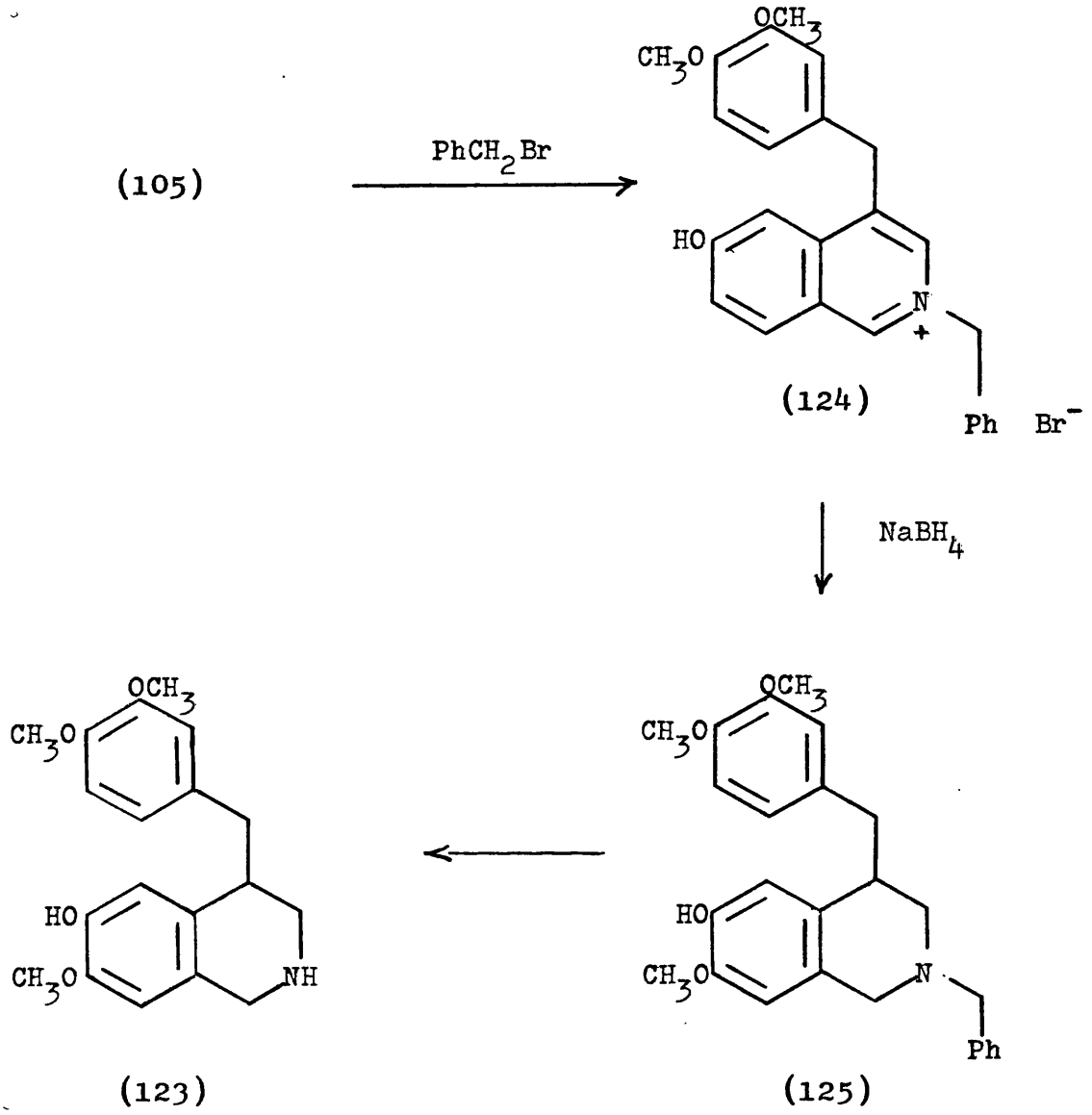
Original attempts to prepare (120) by the route outlined in scheme 14 were hampered by the author's inability to obtain a pure crystalline sample of the fully aromatic isoquinoline (105). Consequently an attempt was made to prepare the required compound by the route outlined in scheme 15.



Scheme 14

The crude fully aromatic isoquinoline (105) obtained from the Bobbit condensation, was treated with benzyl bromide in a large volume of acetone at reflux to afford a poor yield of the N-benzyl bromide (124). Reduction with sodium borohydride in 1:1 aqueous ethanol at 60° afforded the N-benzyl tetrahydroisoquinoline (125) in good yield. However, all attempts to remove the N-benzyl group by hydrogenolysis or by prolonged reflux with 1:1 trifluoroacetic acid-trifluoracetic anhydride failed.

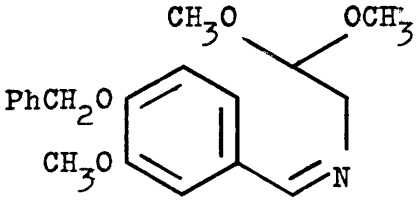
Eventually an improved procedure for the preparation of the fully aromatic isoquinolines afforded a pure crystalline sample of the fully aromatic isoquinoline (105). Equimolar quantities of O-benzylvanillin and aminoacetaldehyde dimethylacetal were heated under partial reflux in benzene. After six hours removal of the solvent afforded the Schiff's



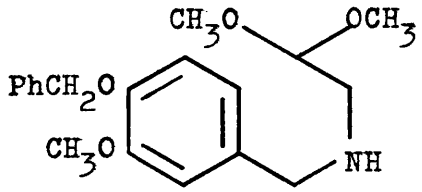
Scheme 16

base (126) which was purified by crystallisation from petroleum ether. Reduction with sodium borohydride afforded the acetal (127) which was purified by recrystallisation from ethanol. The acetal was refluxed in 6M ethanolic hydrochloric acid with a slight excess of veratraldehyde. After 90 minutes the dark red solution was washed with benzene, diluted with a small volume of water and left to stand at room temperature for 3 days, whereupon the hydrochloride (128) crystallised as large red prisms.

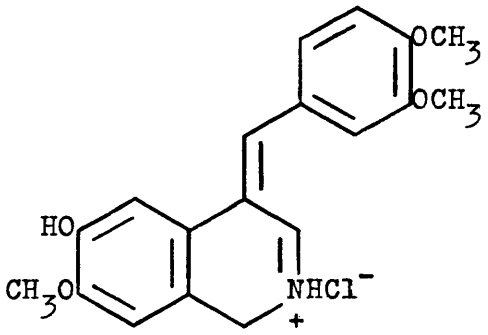
Isomerisation to (105) was achieved by refluxing in ethanol until no further change in the U.V. spectrum was observed. Basification afforded (105) as a beige solid which was crystallised from ethanol.



(126)



(127)

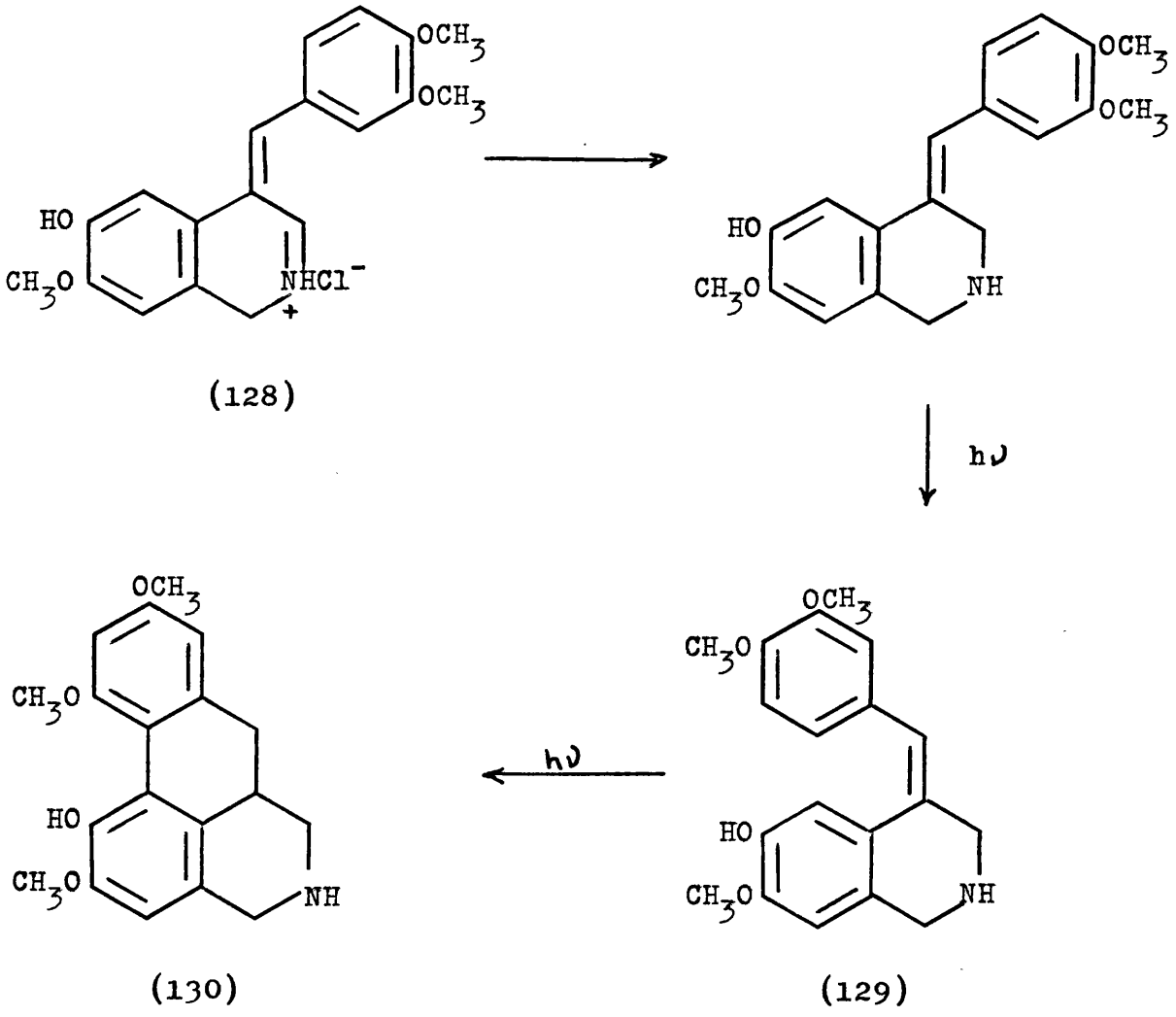


(128)

Attempts to reduce (105) to the required tetrahydro derivative (123) by catalytic hydrogenation were unsuccessful. Refluxing (105) with tin and ethanolic hydrochloric acid[38] afforded a poor yield of a pale yellow crystalline solid whose U.V. spectrum was typical of a 1,2,3,4-tetrahydro-isoquinoline. However the nmr and mass spectrum indicated a mixture from which no pure compound could be obtained. Time did not permit further investigation.

Photochemical preparation of dibenz [de,g] isoquinoline derivatives

The isolation during the course of the previous work of the 4-benzylidine isoquinoline (128) led the author to examine the possibility of synthesising the dibenz [de,g] isoquinoline system by the route outlined in scheme (16). It was believed that by analogy with similar syntheses of the aporphine system[32,33] the triene system of (129) would undergo photochemical cyclisation to give the dibenz [de,g] isoquinoline derivative (130).



(128)

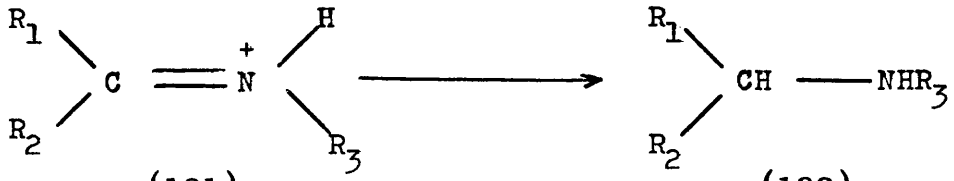
(130)

(129)

Scheme 16

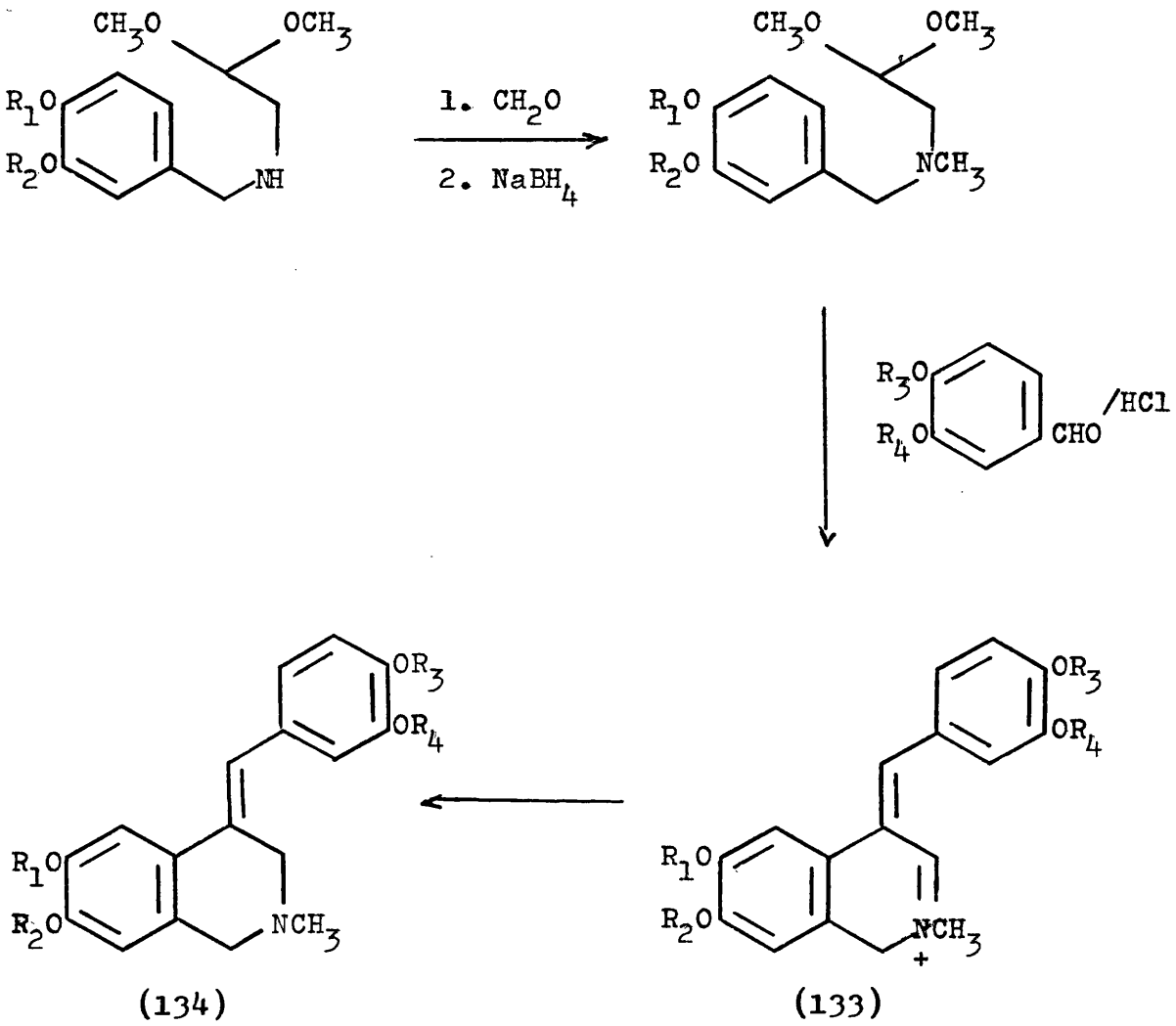
Attempts to reduce the 2,3-double bond of (128) by catalytic hydrogenation or with tin and hydrochloric acid caused isomerisation to the fully aromatic isoquinoline (105).

Borch et al had shown[39] that imminium salts of the type (131) could be reduced to secondary amines (132) by sodium cyanoborohydride at pH 6-7. However, attempts to apply this reaction to the compound (128) again afforded (105) as the major product.



(131) (132)

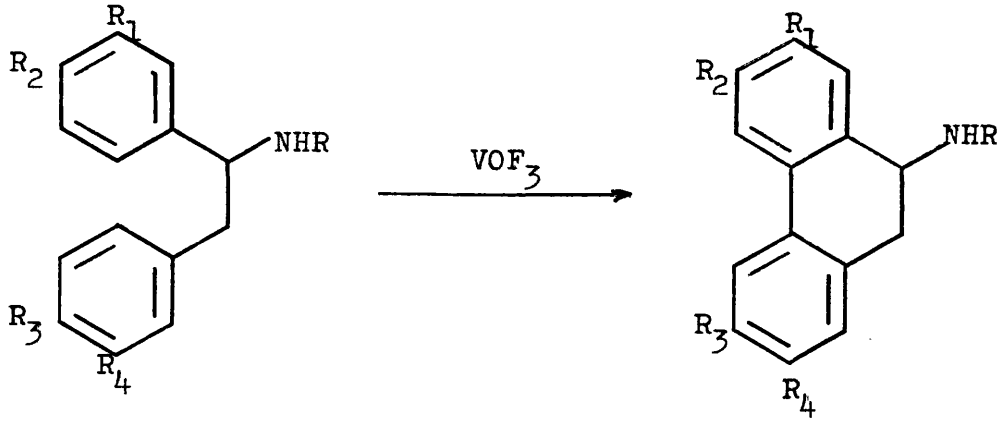
Time did not permit further examination of this synthetic route although it seems probable that the method would be more successful with the N-methyl compounds, prepared as shown in scheme 17. Reduction of an N-methyl-4-benzylidine isoquinoline of the type (133) to the corresponding stilbene (134) has been achieved[35] by adding an intimately ground mixture of the salt and sodium borohydride to absolute ethanol. This procedure could probably be improved by the use of sodium cyanoborohydride.



Scheme 17

Synthesis of 9-aminophenanthrene derivatives

The object of this study was to attempt the synthesis of 9-aminophenanthrene derivatives of the type (136) by intramolecular oxidative aryl-aryl coupling of 1,2-diarylethylamine derivatives (135). The target molecule chosen for this study was the tetramethoxy compound (136 $R_1=R_2=R_3=R_4=OCH_3$), primarily because of the ease with which the required starting 1,2-diarylethylamine derivatives could be prepared.

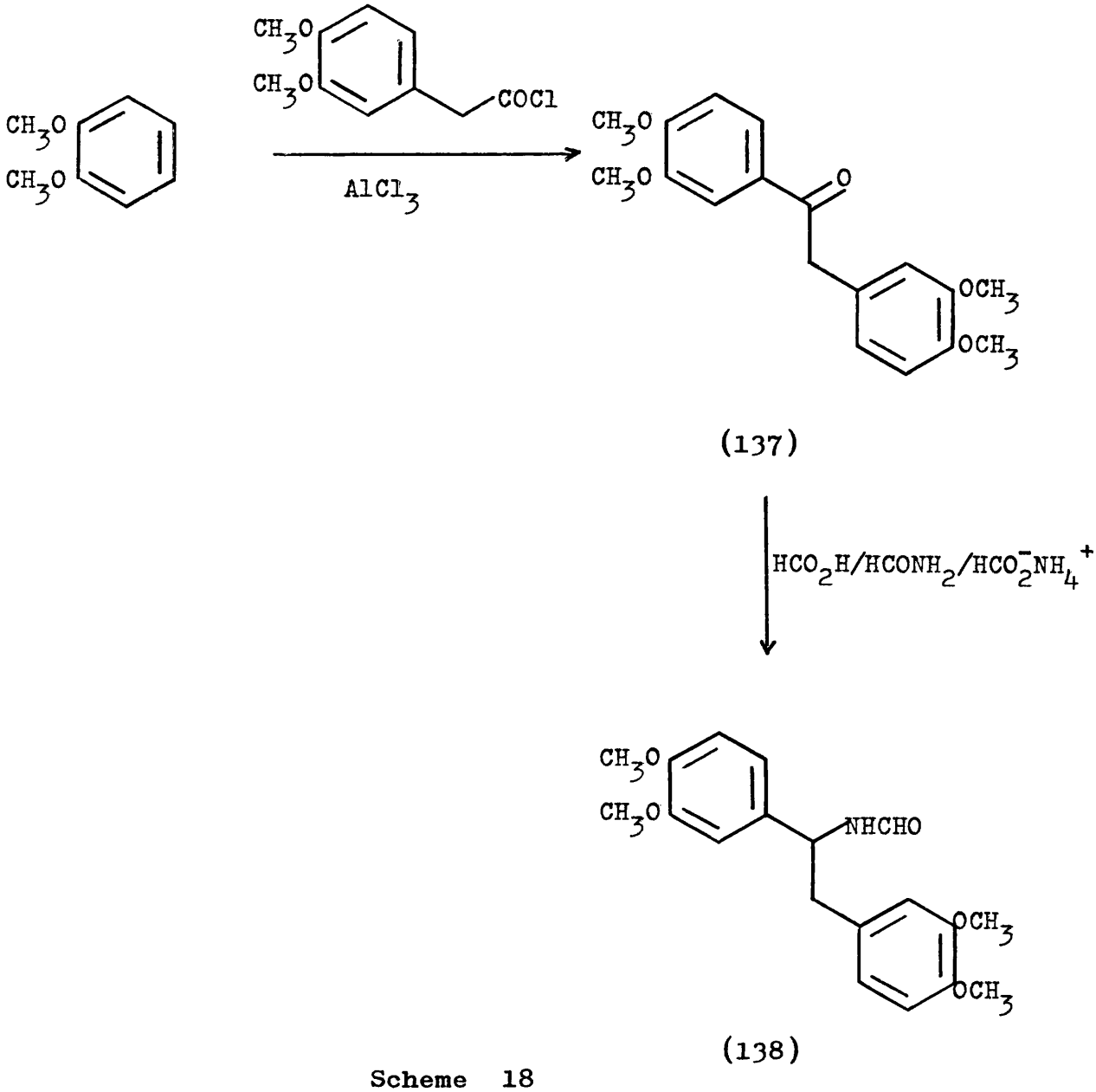


(135) (136)

The first substrate examined was the N-formyl compound (138), prepared by the route outlined in scheme (18)[40]. Friedel crafts acylation of veratrole with 3,4-dimethoxyphenyl-acetyl chloride in the presence of aluminium chloride, afforded the deoxybenzoin (137), which was converted to the N-formyl compound (138) by the Leuckart reaction.

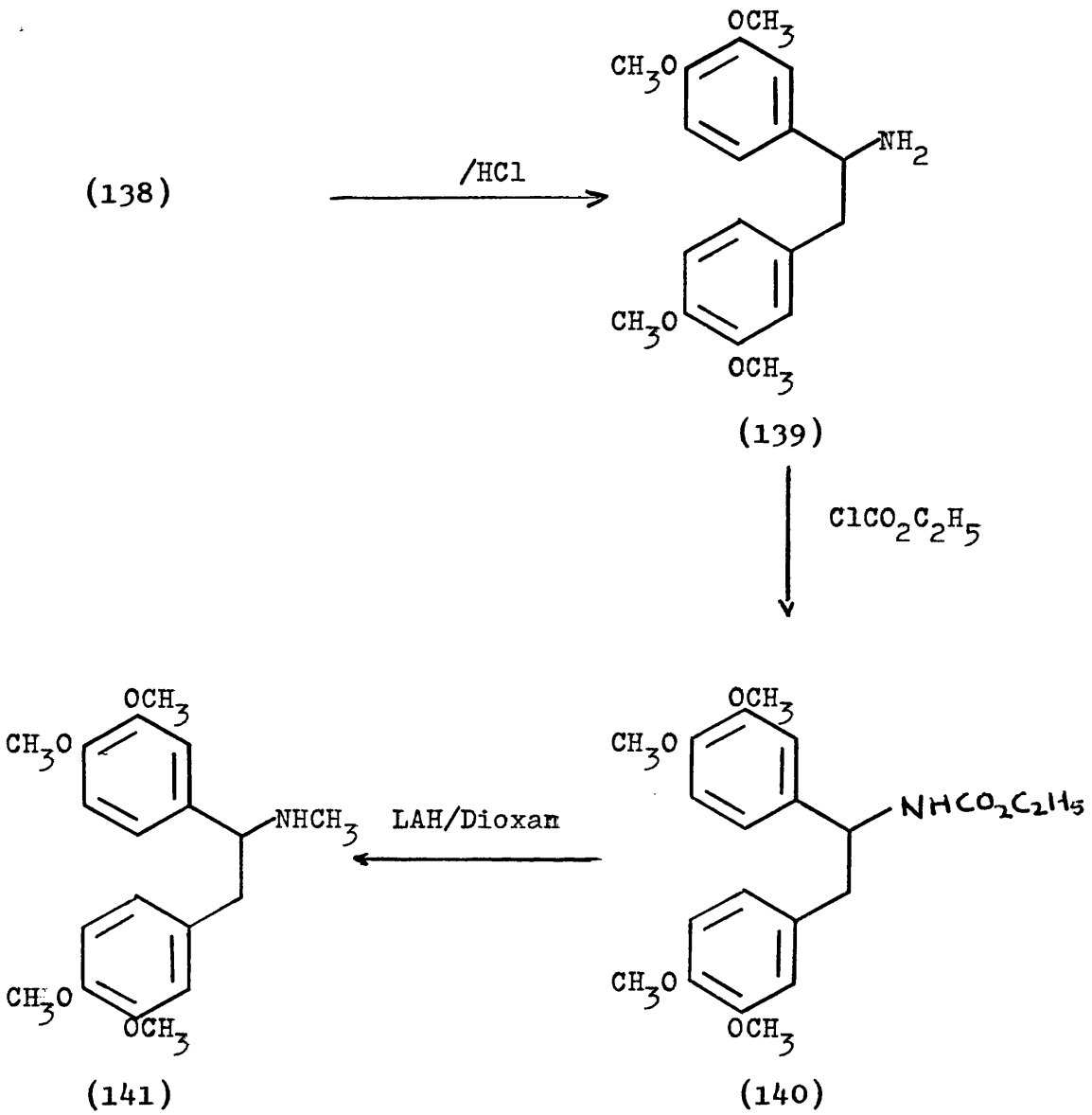
Treatment of the N-formyl compound (138) with VOF_3 for five hours resulted in the formation of a complex mixture from which no identifiable product could be isolated. Similar results were obtained when the reaction time was decreased to 30 or 10 minutes, although, in the latter case a larger proportion of unreacted starting material was present.

The author therefore decided to examine the oxidation of the secondary amine (141). An attempt to prepare this compound by direct reduction of the N-formyl compound (138) with lithium aluminium hydride in boiling dioxan, resulted in the formation of a mixture of the required compound and one other component which could not be separated. The



Scheme 18

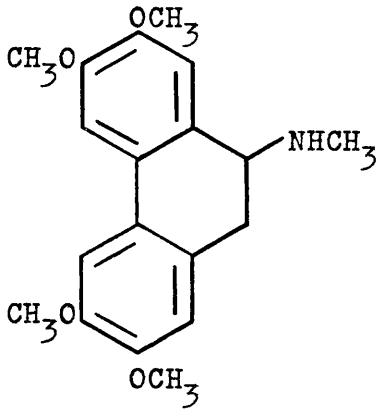
required compound was eventually prepared by the route shown in scheme 19. Hydrolysis of the N-formyl compound afforded the primary amine (139) which was treated with ethyl chloroformate under phase transfer conditions to give the carbamate (140). Reduction with lithium aluminium hydride in boiling dioxan then afforded the required amine (141) as a colourless oil.



Scheme 19

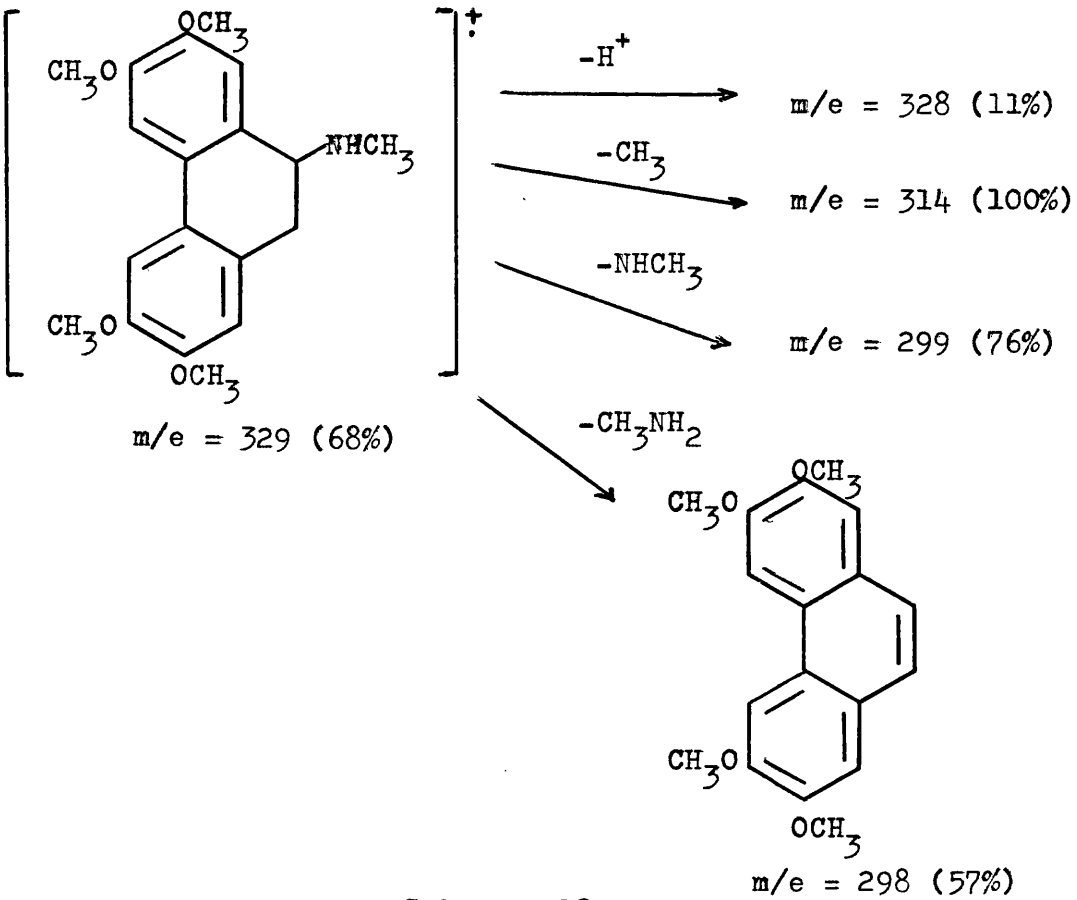
The amine (141) was treated with VOF_3 at -15° for two hours and the crude product crystallised from chloroform to afford a 44% yield of 2,3,6,7-tetramethoxy-9-methylamino-9,10-dihydrophenanthrene (142) as large colourless prisms. The spectral characteristics of the product were consistent with the structure (142). The U.V. spectrum exhibited absorption maxima at 235, 288 and 321 nm and the nmr spectrum showed the presence of four aromatic protons resonating as singlets. That the product was the <u>para-para</u>

coupled compound (142) and not one of the alternative ortho-para or ortho-ortho coupled products, was confirmed by the absence of ortho coupling in the nmr spectrum.



(142)

The mass spectrum could be rationalised in terms of the fragmentations shown in scheme 20 and high resolution mass confirmed a molecular formula of $C_{19}H_{23}NO_4$.



Scheme 20

EXPERIMENTAL

(±) Glaucine (87)

A solution of (±) laudanosine (0.5g 1.4mmole) in 1:1 CH_2Cl_2/TFA(20cm^3) was stirred at -30° under an atmosphere of dry N_2 and a solution of VOF_3 (1.35g 11mmole) in 40:60 ethylacetate TFA added dropwise. On addition of the VOF_3 an instant colour change to dark red was observed. After stirring for 3 hours at -30° the mixture was poured into ice cold H_2O (30cm^3) containing citric acid (5g). Basification with 2M ammonia and extraction with CH_2Cl_2 afforded a brown gum (0.36g). Column chromatography (SiO_2/1% MeOH - $CHCl_3$) afforded glaucine as a brown gum. (18%) λ max (ε) 233 (13,600), 281 (8,100), 301 (8,000). Nmr ($CDCl_3$) 8.11 s [1] , 6.92 s [1] and 6.81 s [1] (Ar-H), 4.32 t [1] (C$_1$-H) 3.94 s and 3.91 s [9] (3xOCH_3), 3.68 s [3] (OCH_3), 2.60 s [3] (N-CH_3).

N-benzylaminoacetaldehydedimethylacetals

Amino acetaldehydedimethylacetal (10.5g) and the aldehyde (0.1 mole) were stirred in EtOH at room temperature for 24 hours. $NaBH_4$ (2.0g) was added portionwise and the mixture stirred for a further 24 hours. Water (400cm^3) was added and the mixture extracted with CH_2Cl_2 (2x100cm^3, 1x50cm^3). After washing with H_2O (50cm^3), the extracts were dried (Na_2SO_4) and evaporated to yield the acetal. Excess aminoacetaldehydedimethylacetal was distilled off at 70° and 1 mm pressure.

a) N-(3,4-dimethoxybenzyl)aminoacetaldehydedimethyl acetal (90)

Colourless oil (95%). Nmr ($CDCl_3$) 6.9 [3] (Ar-H), 4.55 t J=5Hz [1] ($C\underline{H}(OCH_3)_2$), 3.9 s [6] ($2xOCH_3$), 3.8 s [2] (Ar-$C\underline{H}_2$-NH), 3.4 s [6] ($CH(OC\underline{H}_3)_2$), 2.78 d J=5Hz 2 ($C\underline{H}_2$-CH), 1.77 s [1] (NH) removed by D_2O.

b) N-(3-methoxy-4-benzyloxybenzyl)aminoacetaldehyde-dimethyl acetal

Red oil (76%). Nmr ($CDCl_3$) 7.5-7.2 complex [5] ($\underline{Ph}$-CH_2), 6.90 s [1] , 6.79 s [2] (Ar-H), 5.11 s [2] (Ph-$C\underline{H}_2$-), 4.47 t J=5Hz [1] ($C\underline{H}(OCH_3)_2$), 3.87 s [3] (OCH_3), 3.72 s [2] (Ar-$C\underline{H}_2$-N), 3.35 s [6] ($CH(OC\underline{H}_3)_2$), 2.73 d J=5Hz [2] ($C\underline{H}_2$-CH$<$), 1.76 broad s [1] (NH) removed by D_2O.

c) N-(3-hydroxy-4-methoxybenzyl)aminoacetaldehyde-dimethyl acetal

Brown solid (81%). Nmr ($CDCl_3$) 6.89 broad s [1] and 6.8 s [2] (Ar-H), 4.47 t J=5Hz [1] ($C\underline{H}(OCH_3)_2$), 3.83 s [3] (OCH_3), 3.69 s [2] , (Ar-$C\underline{H}_2$-N), 3.34 s [6] ($CH(OC\underline{H}_3)_2$), 2.72 d J=5Hz [2] ($C\underline{H}_2$-CH), 4.0-3.8 [2] removed by D_2O (NH and OH).

4-benzyl-isoquinoline methiodides

The N-benzylaminoacetaldehydedimethyl acetal (0.02 mole) and the aldehyde (0.024 mole) were dissolved in EtOH ($40cm^3$) and cHCl ($40cm^3$) added. The mixture was refluxed at 100^o for 90 minutes, allowed to cool and poured into water ($400cm^3$). After washing with C_6H_6 ($3x50cm^3$) the mixture was made strongly basic with 30% NaOH and warmed. Upon cooling the pH was adjusted to 8-9 and the mixture extracted with CH_2Cl_2 ($3x100cm^3$). Evaporation of the dried

(Na_2SO_4) extracts afforded the isoquinolines as brown gums. The products were without purification dissolved in acetone ($150cm^3$) at reflux and methyliodide (100% excess) added. After refluxing for five minutes the mixtures were allowed to cool to room temperature, whereupon the required methiodides crystallised.

a) 4-(3,4-dimethoxybenzyl)-6,7-dimethoxyisoquinoline methiodide (92)

Orange microcrystalline solid (46.6%) mp 204-208° ex EtOH. Nmr ($CDCl_3$/DMSO) 9.76 s [1] (C_1-H), 8.37 s [1] , (C_3-H) 7.85 s, 7.52 s, 6.97 s and 6.88 s [5] (Ar-H), 4.49 s [3] ($\overset{+}{N}$-CH_3), 4.46 s [2] (Ar-$\underline{CH}_2$), 4.06 s [6] (2xOCH_3), 3.82 s [6] (2xOCH_3). (Found: C,52.5; H, 5.1; N, 2.8; $C_{21}H_{24}NO_4I$ requires C, 52.4; H, 5.0; N, 2.9%)

b) 4-(3,4-dimethoxybenzyl)-6-hydroxy-7-methoxyisoquinoline methiodide (104)

Light brown microcrystalline solid (21%) mp 169-171 d ex EtOH. Nmr ($CDCl_3$/DMSO) 9.67 broad s [1] (C_1-H), 8.3-6.6 complex [7] (6xAr-H+OH removed by D_2O), 4.47 s [3] ($\overset{+}{N}$-CH_3), 4.31 s [2] (Ar-CH_2), 4.08 s [3] (OCH_3) and 2.86 s [6] (2xOCH_3). (Found: C, 51.9; H, 4.8; N, 2.9; $C_{20}H_{22}NO_4I$ requires C, 51.4; H, 4.7; N, 2.9%).

c) 4-(3-hydroxy-4-methoxybenzyl)-6,7-dimethoxyisoquinoline methiodide

Yellow needles (22%). Nmr ($CDCl_3$/DMSO) 9.7 s [1] (C_1-H), 8.5-6.6 m [7] (6xAr-H+OH removed by D_2O), 4.48 s [3] ($\overset{+}{N}$-CH_3), 4.36 s [2] (Ar-$\underline{CH}_2$), 4.05 s [6] , (2xOCH_3), 3.83 s [3] (OCH_3).

d) 4-(3,4-dimethoxybenzyl)-6-methoxy-7-hydroxy isoquinoline methiodide

Green-brown needles (46%) mp 156-165° d nmr ($CDCl_3$/DMSO) 9.57 broad s [1] (G-H), 8.4-6.7 m [1] (6xAr-H and OH removed by D_2O), 4.47 broad s [5] ($\overset{+}{N}-CH_3$ and Ar-$\underline{CH}_2$), 4.07 s [3] (OCH_3), 3.85 s [6] ($2xOCH_3$).

e) 4-(3-methoxy-4-hydrocybenzyl)-6,7-dimethoxyisoquinoline methiodide

Beige microcrystalline solid (37%) mp 175° nmr ($CDCl_3$DMSO) 9.78 s [1] (G-H), 8.63 broad s [1] removed by D_2O (OH), 8.38 s [1] (C_3-H), 7.86 s [1] 7.54 s [1] , 7.0-6.6 complex [5] (Ar-H), 4.50 s [3] ($\overset{+}{N}-CH_3$), 4.43 s [2] (Ar-$\underline{CH}_2$), 4.06 s [6] ($2xOCH_3$), 3.81 s [3] (OCH_3).

f) 4-(3,4-methylenedioxybenzyl)-6-hydroxy-7-methoxy isoquinoline methiodide

Light brown needles (43%) mp 178-183° d nmr ($CDCl_3$/ DMSO) 9.51 s [1] (G-H), 8.12 s [1] (C_3-H), 7.7 fine d [1] (Ar-H), 7.4 s [1] (Ar-H), 6.7 d [3] (3xAr-H), 5.91 s [2] ($\underline{CH}_2O_2$), 4.40 s 3 ($\overset{+}{N}-CH_3$), 4.20 s [2] (Ar-CH_2), 4.03 s [3] (OCH_3).

2-methyl-4-benzyl tetrahydroisoquinolines

The 4-benzylisoquinoline methiodide (2g) was dissolved in hot 1:1 EtOH/H_2O ($100cm^3$) and $NaBH_4$ (1.5g) was added portionwise with stirring. After stirring overnight at room temperature the mixture was made acid with dilute HCl to decompose excess $NaBH_4$ and N-boranes . The pH was adjusted to 8-9 with dilute NH_3. Extraction with C_6H_6 ($3x50cm^3$) and evaporation of the dried (Na_2SO_4) extracts

afforded the required tetrahydroisoquinolines as colourless oils which crystallised from EtOH as white solids.

a) N-methyl-4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (88)

White needles (92%) mp 96-98° ex EtOH. λ max (ε) 234 (17,100), 283 (8,000). nmr ($CDCl_3$) 6.9-6.6 m [3] (Ar-H) 6.5 s [2] (Ar-H), 3.82 s [9] ($3xOCH_3$), 3.78 s [2] (C_4-CH_2), 3.71 s [3] (OCH_3), 3.6-2.4 complex [5] (aliphatics), 2.34 s [3] (N-CH_3). Mass (m/e) 357 (M^+) [43%], 356 (M^+-1) [27%], 342 [12%], 326 [5%], 314 [8%], 309 [28%], 283 [26%], 268 [9%], 219 [40%], 206 [92%], 205 [100%], 204 [95%], 151 [26%]. (Found: C, 70.1; H, 7.3; N, 3.9; $C_{21}H_{27}NO_4$ requires C, 70.6; H, 7.6; N, 3.9%)

b) N-methyl-4-(3,4-dimethoxybenzyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (102)

White needles (90%) mp 140-142° ex EtOH λ max (ε) 230 (14,000), 286 (6,500). On addition of NaOH λ max (ε), 226 (18,300), 288 (5,000), 304 (5,500). nmr ($CDCl_3$), 6.94-6.66 m [4] (Ar-H), 6.52 s [1] (Ar-H), 5.8 broad s [1] removed by D_2O (OH), 3.88 s and 3.83 s [9] ($3xOCH_3$), 3.8-2.4 complex [7] (aliphatics) 2.37 s [3] (N-CH_3). Mass m/e 343 (M^+) [26%], 342 $(M-1)^+$ [15%], 328 [10%], 312 [3%], 300 [5%], 285 [10%], 269 [12%], 254 [4%], 205 [16%], 192 [73%], 191 [91%], 190 [100%], 151 [85%]. (Found: C,69.9; H, 7.1; N, 4.2; $C_{20}H_{25}NO_4$ requires C, 70.0; H, 7.3; N, 4.1%)

c) N-methyl-4-(3-hydroxy-4-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (110a)

White needles (81%) 139-143° λ max (ε) 234 (11,200),

285 (6,600). On addition of NaOH λ max (ε) 233 (12,700), 293 (7,800). Nmr ($CDCl_3$), 6.9-6.4 complex [5] (Ar-H), 3.87 s, 3.85 s and 3.77 s [10] ($3xOCH_3$+OH removed by D_2O), 3.76-2.44 complex [7] (aliphatics), 2.40 s [3] ($N-CH_3$) Mass m/e 343 (M^+) [8%], 342 (M^+-1), [4%], 312 [2%], 300 [10%], 285 [15%], 269 [6%], 254 [3%], 239 [2%], 225 [4%], 219 [16%], 206 [89%], 205 [100%], 204 [93%], 137 [27%]. (Found: C, 70.1; H, 7.2; N, 4.2; $C_{20}H_{25}NO_4$ requires C, 70.0; H, 7.3; N, 4.1%).

d) N-methyl-4-(3,4-dimethoxybenzyl)-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (110b)

White needles (78%) mp 139-140° λ max (ε) 239 (16,100), 285 (7,600). On addition of NaOH λ max (ε), 233 (15,800), 254 (14,300), 288 (7,200), 300 sh (6,050). Nmr ($CDCl_3$), 7.0-6.66 complex [3] (Ar-H), 6.57 s [1] (Ar-H), 6.54 s [1] (Ar-H), 3.90 s [6] ($axOCH_3$), 3.77 s [3] (OCH_3), 3.7-2.4 complex [7] (aliphatics) 2.39 s [3] ($N-CH_3$) Mass m/e 343 (M^+) [7%], 342 (M^+-1) [5%], 328 [3%], 325 [3%], 312 [1%], 310 [1%], 300 [2%], 285 [7%], 269 [7%], 254 [4%], 205 [19%], 192 [78%], 191 [100%], 190 [89%], 151 [24%]. (Found: C,70.1; H, 7.4; N, 4.1; $C_{20}H_{25}NO_4$ requires C, 70.0; H, 7.3; N 4.1%).

e) N-methyl-4-(3-methoxy-4-hydroxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (110c)

Colourless prisms (100%) mp 123-125° λ $max_{\uparrow}^{(\varepsilon)}$ 237 (16,500) 284 (10,100). On addition of NaOH λ $max_{\uparrow}^{(\varepsilon)}$ 241 (16,500) 292 (10,600). Nmr ($CDCl_3$) 6.9-6.6 complex [3] (Ar-H), 6.47 s [2] (Ar-H), 5.88 broad [1]removed by D_2O (OH), 3.78 s [6]

($2xOCH_3$), 3.70 s [3] (OCH_3), 3.7-2.3 complex [7] (aliphatics), 2.34 s [3] ($N-CH_3$). Mass m/e 343 (M^+) [67%], 342 $(M-1)^+$ [21%], 328 [10%], 312 [5%], 300 [13%], 285 [19%], 269 [7%], 254 [2%], 220 [31%], 206 [100%], 205 [66%], 204 [51%] m^* 271, 202. (Found: C,70.1; H, 7.2; H, 4.2, $C_{20}H_{25}NO_4$ requires C, 70.0; H, 7.3; N, 4.1%).

f) N-methyl-4-(3,4-methylenedioxybenzyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (110d)

Pale yellow crystalline solid (64%) λ max (ε) 235 (12,000), 289 (10,100). On addition of NaOH λ max (ε) 235 (13,400), 298 (10,700). Nmr ($CDCl_3$), 6.84-6.56 [4] (Ar-H), 6.5 s [1] (Ar-H), 5.92 s [2] ($C\underline{H}_2O_2$), 5.52 broad s [1] removed by D_2O (OH), 3.8 s [3] (OCH_3), 3.74-2.40 complex [7] (aliphatics), 2.37 s [3] ($N-CH_3$). Mass m/e 327 (M^+) [41%], 326 (M^+-1) [17%], 312 [77%], 284 [11%], 269 [26%], 254 [9%], 239 [7%], 205 [27%], 192 [78%], 191 [93%], 190 [100%], 135 [39%].

General Procedure for VOF_3 oxidations

Solvents: Dichloromethane was dried by distillation from calcium hydride. Ethylacetate was dried by passing through a column of silica gel conditioned at 110° for 24 hours.

The substrate (0.5 g) as a 0.05 M solution in CH_2Cl_2 containing 20% TFA-TFAA (20:1) was stirred at -15° (ice/salt) under an atmosphere of N_2. VOF_3 (2.5 molar equivalents) dissolved in the minimum volume of 1:1 ethylacetate/TFA-TFAA (20:1) was added dropwise. When reaction was complete the resultant metallic blue solution was poured into an ice cold solution of citric acid (5 g) in water ($30cm^3$).

The pH was adjusted to 8-9 with dilute ammonia and the organic layer separated. The blue aqueous layer was extracted with CH_2Cl_2 ($3x30cm^3$) and the combined organic extracts washed with H_2O ($30cm^3$) and dried (Na_2SO_4). Evaporation of the extracts afforded the crude products as brown tars.

Oxidation of N-methyl-4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (88)

Column chromatography ($SiO_2/CHCl_3$) afforded an orange solid (48 mg, 9.6%). Rf 0.65 (SiO_2/10% MeOH-$CHCl_3$) mp 106 d λ max 240,273, 450. Nmr ($CDCl_3$) 9.68 s [1] , 8.87 s [1] , 7.33 s [1] , 7.26 s [1] , 6.5 s [1] , 4.2-3.4 complex including four singlets at 4.12, 4.04, 3.86 and 3.54 (aliphatics). Mass m/e 351 (M^+) [88%] , 320 (M^+-31) [100%]. Attempts to crystallise this product were unsuccessful.

Further elution afforded the required dibenz [de,g] isoquinoline derivative (89) as a brown oil (189 mg 38%). Rf 0.50 (SiO_2/10% MeOH - $CHCl_3$). The product was dissolved in 2 M HCl ($5cm^3$) and the solution washed with CH_2Cl_2 ($2cm^3$). Basification (2 M ammonia) and extraction with CH_2Cl_2 ($3x5cm^3$) reafforded the free base which precipitated as a beige solid upon trituration with Et_2O mp 112-114° λ max (ε) 235 (19,800), 281 (14,600), 305 (13,300). Nmr ($CDCl_3$) 8.17 s [1] (Ar-H), 6.75 s [1] (Ar-H), 6.54 s [1] (Ar-H), 3.89 s [6] ($2xOCH_3$), 3.84 s [3] (OCH_3), 3.65 s [3] (OCH_3), 3.9-2.00 complex [7] (aliphatics), 2.46 s [3] (NCH_3). Mass m/e 355 (M^+) [57%] , 313 [15%] , 312 [67%] , 298 [15%] , 297 [70%] , 282 [32%] , 281 [100%] ,

269 [11%] , 265 [11%] , 254 [12%] , 250 [14%] m* 283, 274, 253. (Found: C, 69.0; H, 6.7; N, 3.9; $C_{21}H_{25}NO_4$ requires C, 71.0; H, 7.1; N, 3.9%).

Treatment of dilute acetone solution of the product with 2 drops of conc. HCl afforded the hydrochloride as pale orange needles mp 215-218°. (Found: C, 64.6; H, 6.9; N, 3.5; $C_{21}H_{26}NO_4Cl$ requires C; 64.4; H,6.6; N, 3.6%).

Oxidation of N-methyl-4-(3,4-dimethoxybenzyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (102)

The crude product (0.43 g) was subjected to column chromatography (Al_2O_3/10% C_6H_6 -$CHCl_3$) to afford the dibenz [de,g] isoquinoline derivative (106) as a brown gum (367 mg, 67%). Rf 0.4 (SiO_2/10% MeOH - $CHCl_3$). The product was dissolved in 2M HCl (5cm^3) washed with CH_2Cl_2 (2cm^3). Basification to pH 8-9 with dilute ammonia and extraction with CH_2Cl_2 reafforded the free base which crystallised from EtOH as colourless prisms. Mp 148-151° λ max (ε) 233 (20,800), 281 (12,800), 305 (13,300). On addition of NaOH λ max (ε), 233 (21,000), 270 (10,900), 311 (6,000), 344 (8,200). Nmr ($CDCl_3$) 8.21 s [1] (Ar-H), 6.83 s [1] (Ar-H), 6.55 s [1] (Ar-H), 3.95 s [6] (2xOCH_3), 3.90 s [3] (OCH_3), 3.9-2.0 complex [8] (aliphatics + OH), 2.47 s [3] (N-CH_3). Mass m/e 341 (M^+) [86%] , 340 (M^+-1) [25%] , 298 [90%] , 299 [18%] , 297 [14%] , 283 [28%] , 267 [100%] , 268 [20%] , 266 [20%] , m* 260, 230, 240. (Found: C, 70.7; H, 6.7; N, 4.1% $C_{20}H_{23}NO_4$ requires C, 70.4; H, 6.8; N, 4.1%).

Further elution with 5% MeOH in $CHCl_3$ afforded (107) (61 mg 12%) Rf 0.16 (SiO_2/10% MeOH - $CHCl_3$). The product

crystallised from $CHCl_3$ as large colourless hexagonal prisms which became opaque orange upon vacuum drying at room temperature. The product melted to a red gum over the range 96-100°, resolidified over the range 130-140° and then remelted at 145°. λ max (ε) 231 (19,500), 278 (16,200), 321 (14,700), 331 (14,300), 446 (22,600). Nmr 8.79 s [1] (C_4-H), 7.13 s [1] 6.50 s [1] and 6.21 s [1] (3xAr-H), 3.90 s [3], 3.80 s [3] and 3.70 s [3] (3xOCH_3), 3.2 s [2] (-$\underline{CH_2}$-$\overset{+}{N}$), 3.13 s [3] ($\overset{+}{N}$-CH_3), 4.39 d J=9Hz [2] ($C\underline{H_2}$-CH), 2.42 s [1] removed by D_2O (OH). Mass m/e 341 [48%], 340 [34%], 339 [100%], 338 [45%], 324 [20%], 298 [51%], 283 [11%], 267 [52%] m* 309.7, 268.75, 260.4, 239.2.

Oxidation of the dibenz [de,g] isoquinoline derivative (106)

The dibenz [de,g] isoquinoline derivative (106) (30 mg) was subjected to further oxidation with VOF_3 under the conditions previously described to afford a product identical with, TLC and UV (107). Rf 0.16 (SiO_2/10% MeOH - $CHCl_3$) λ max 231, 278, 321, 331, 446.

Reduction of (107)

The minor product from the oxidation of (102) (5 mg) was dissolved in 1:1 EtOH-H_2O (1cm^3) and treated with $NaBH_4$ (3 mg). The yellow colour of the solution was instantaneously discharged. After standing overnight the solution was made acid with dil. HCl to decompose boranes and the pH adjusted to 8-9 with dil. ammonia. Extraction with CH_2Cl_2 (2x1cm^3) and evaporation of the dried (Na_2SO_4) extracts afforded a product identical, TLC, UV and Mass with the dibenz [de,g] isoquinoline derivative (106).

Rf 0.4 (SiO_2, 10% MeOH in $CHCl_3$). λ max 233, 282, 305. On addition of NaOH λ max 233, 270, 311, 344. Mass m/e 341 (M^+) [94%], 340 $(M-1)^+$ [28%], 298 [96%], 267 [100%].

4-(3,4-dimethoxybenzyl)-6-hydroxy-7-methoxyisoquinoline benzyl bromide (124)

Crude 4-(3,4-dimethoxybenzyl)-6-hydroxy-7-methoxy-isoquinoline from the Bobbit condensation (page 185) (4.6 g) was dissolved in acetone (200 cm^3) at reflux and the filtered hot solution treated with benzyl bromide (50% excess). After refluxing for 15 minutes the solution was left to stand at room temperature overnight whereupon the required compound crystallised as orange needles (18%) mp 192-193°. Nmr (TFA) 9.28 s [1] (C_1-H), 7.84 s [1] (C_3-H), 7.8-6.8 complex [11] (10xAr-H+OH), 5.74 s [2] (Ph-$\underline{CH_2}$-$\overset{+}{N}$), 4.39 s [2] (Ar-$\underline{CH_2}$), 4.2 s [3], 3.98 s [3], 3.84 s [3] (3xOCH_3).

N-benzyl-4-(3,4-dimethoxybenzyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (125)

The above bromide (1.3 g) was dissolved in hot 1:1 EtOH-H_2O (50cm^3) and $NaBH_4$ (0.5 g) added portionwise with stirring. After stirring overnight at room temperature the solution was made acid with dil. HCl to decompose excess borohydride and N-boranes. The pH was adjusted to 8-9 amd the mixture extracted with C_6H_6 (3x50cm^3). The extracts were washed with H_2O (50cm^3), dried (Na_2SO_4) and evaporated to afford the product as a yellow oil (87%) which could not be persuaded to crystallise from a number of solvents λ max (ε) 235 (15,900) 285 (9,400). On

addition of NaOH λ max (ε) 236 (18,000), 288 (8,400), 304 (8,200). Nmr ($CDCl_3$) 7.5-7.1 complex [5] (Ar-H), 6.9-6.4 complex [5] (Ar-H), 3.82 s [3] and 3.78 s [6] (3 x OCH_3) 3.7-2.2 [10] (aliphatics + OH) including 2.88 s [2] (N-$\underline{CH}_2$-Ph).

N-(4-benzyloxy-3-methoxybenzal) aminoacetaldehyde-dimethylacetal (126)

O-benzylvanillin (15 g) and aminoacetaldehyde-dimethylacetal (6.5 g) were heated in dry C_6H_6 ($80cm^3$) under a Dean and Stark head for 5 hours. The solvent was removed and the residue crystallised from pet. ether (b.p. 60-80°) to give white prisms (88%) mp 57.5-60°. Nmr ($CDCl_3$) 8.15 s [1] (CH=N) 7.5-7.2 complex [6] ($\underline{Ph}$-CH_2 and Ar_2-H), 7.1 dd [1] J ortho = 8Hz, J meta = 2Hz (Ar_6-H), 6.87 d [1] J ortho = 8Hz (Ar_5-H) 5.17 s [2] ($PhCH_2O$), 4.65 t [1] J = 5Hz ($\underline{CH}(OCH_3)_2$), 3.92 s [3] (OCH_3) 3.73 d [2] J = 5 Hz (CH-$\underline{CH}_2$), 3.41 s [6] (CH($O\underline{CH}_3$)$_2$).

N-(4-benzyloxy-3-methoxybenzyl)aminoacetaldehydedimethyl acetal (127)

$NaBH_4$ (3.0 g) was added portionwise to a stirred solution of the above benzalaminoacetal (17.4 g) in EtOH ($150cm^3$). After stirring overnight at room temperature the solvent was removed and H_2O ($200cm^3$) was added to the residue. Extraction with CH_2Cl_2 ($3x100cm^3$) afforded, upon evaporation of the dried (Na_2SO_4) extracts the title compound as a colourless oil (100%). Nmr ($CDCl_3$) 7.52-7.20 complex [5] ($\underline{Ph}$-CH_2), 6.90 s [1] and 6.79 s [2] (3xAr-H), 5.10 s [2] (Ph-CH_2) 4.47 t [1] J = 5Hz (CH_2-CH), 3.87 s [3] (OCH_3),

3.72 s [2] (-$\underline{CH_2}$-NH), 3.35 s [6] (CH(O$\underline{CH_3}$)$_2$), 2.77 d [2] J = 5Hz ($\underline{CH_2}$-CH) 1.76 broad s [1] removed by D_2O (NH)

4-(3,4-dimethoxybenzylidine)-6-hydroxy-7-methoxy-1,4-dihydroisoquinoline, hydrochloride (128)

The above benzylaminoacetal (17.3g) and veratraldehyde (10.8g) were dissolved in EtOH (100cm^3) and conc. HCl (100cm^3) added. The mixture was refluxed on a steam bath for 30 minutes, diluted with H_2O (60cm^3), washed with C_6H_6 (2x50cm^3) and left to stand at room temperature for 48 hours whereupon the product crystallised as large red prisms (59%) mp isomerised to (105) 150-165° λ max (ε) 236 (15,900), 275 (11,3000, 305 (10,400), 366 (11,300). On addition of NaOH λ max (ε) 246 (20,300), 301 (11,000), 342 (11,900) nmr (TFA) 8.95 d [1] J = 9Hz (C_3-H), 8.39 broad s [1] (Ar-$\underline{CH}$=C), 7.54 s [1] , 7.18 s [3] , 6.88 s [1] (5xAr-H), 5.17 broad s [2] (CH_2-$\overset{+}{N}$) 4.02 s [9] (3xOCH_3).

4-(3,4-dimethoxybenayl)-6-hydroxy-7-methoxy-isoquinoline (105)

The product from the above reaction (5g) was refluxed in EtOH (100cm^3) until the UV spectrum indicated that isomerisation was complete. Evaporation afforded a yellow residue which was dissolved in H_2O (100cm^3). The pH was adjusted to 8 and the precipitate collected and recrystallised from EtOH. Beige plates (100%) mp 194-199° d λ max (ε) 242 (69,700), 283 (15,150), 313 (8,300), 327 (6,400). On addition of NaOH λ max (ε) 222 (54,500), 253 (62,100), 340 (15,100). Nmr ($CDCl_3$/DMSO) 8.9 s [1] (C_1-H), 8.16 s [1] (C_3-H), 7.36-6.64 m [5] (Ar-H), 4.16 s [2] (C_4-CH_2), 3.99 s [3] (OCH_3), 3.77 s [6] (2xOCH_3).

3,4-dimethoxyphenylacetylchloride

Redistilled $SOCl_2$ (19.0g) was added to a stirred solution of 3,4-dimethoxyphenylacetic acid (21.0g) in dry C_6H_6 ($250cm^3$) at room temperature. After stirring for 40 minutes at room temperature, the mixture was refluxed for 90 minutes. The solvent and excess $SOCl_2$ were removed at reduced pressure to afford the required product as a red oil (92%) ν max 2850, 1800, 1030.

3,4-dimethoxy-(3,4-dimethoxybenzyl)-phenone (137)

3,4-dimethoxyphenylacetylchloride (22.7g) and veratrole (35g) were dissolved in CH_2Cl_2 ($150cm^3$) and $AlCl_3$ (42g) was added portionwise with stirring. After refluxing for 2 hours, the mixture was allowed to cool and then poured into a mixture of crushed ice (150g), H_2O ($35cm^3$) and conc. HCl ($75cm^3$). CH_2Cl_2 ($100cm^3$) was added and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 ($3x50cm^3$) and the combined organic extracts dried (Na_2SO_4) and evaporated to afford the required product as a red oil which crystallised upon cooling. The product crystallised from EtOH as beige needles (78%) mp 98-100°. Nmr ($CDCl_3$) 7.74-7.5 m, 6.91 s, 6.8 s [6] (Ar-H), 4.14 s [2] ($CO-C\underline{H}_2$) 3.9 s [3] , 3.88 s [3] , 3.83 s [6] ($4xOCH_3$).

N-formyl-1,2-bis(3,4-dimethoxyphenyl)-ethylamine (138)

The above deoxybenzoin (11.5g), formamide ($100cm^3$) 90% formic acid ($50cm^3$) and ammonium formate (25g) were refluxed for 9 hours. The cooled solution was poured into H_2O ($100cm^3$) and the white precipitate filtered off, washed with H_2O and recrystallised from MeOH (81%). White needles

mp 138-140° λ max (ε) 237 (13,100) 280 (6,000), ν max 3340, 1657. Nmr ($CDCl_3$) 8.15 s [1] (CHO) 6.9-6.44 complex [6] (Ar-H), 6.08 d J = 8Hz [1] (NH), 5.25 dd J = 7Hz (CH_2-$\underline{CH}$) 3.83 s, 3.80 s, 3.78 s, 3.73 s [12] (4xOCH_3), 3.04 d J = 7Hz [2] ($\underline{CH_2}$-CH).

1,2-bis(3,4-dimethoxyphenyl)-ethylamine (139)

The above N-formyl compound (10g) was dissolved in 2M HCl (500cm^3) and refluxed for 30 minutes to give a clear yellow solution. Upon cooling the solution was washed with Et_2O (2x100cm^3), basified (NaOH) and the precipitated solid collected and recrystallised from EtOH. White needles (56%) mp 104-105°. Nmr ($CDCl_3$) 7.0-6.6 complex [6] (Ar-H), 4.13 dd [1] J_1 = 8Hz, J_2 = 5Hz ($\underline{CH}$-CH_2), 3.89 s, 3.83 s [12] (3xOCH_3), 2.86 m [2] ($C\underline{H_2}$-CH) 1.47 broad s [2] removed by D_2O (NH_2).

N-carbethoxy-1,2-bis-(3,4-dimethoxyphenyl)-ethylamine (140)

The above primary amine (5.0g) was stirred with 2M NaOH (30cm^3) and Et_2O (60cm^3) and ethyl chloroformate (3.5cm^3) added dropwise. After stirring for 2 hours the ether was evaporated and the product filtered off and crystallised from MeOH. White needles (84%) mp 132-133° Nmr ($CDCl_3$) 7.0-6.4 complex [6] (Ar-H) 5.1-4.7 complex [2] (CH_2-$\underline{CH}$+$\underline{NH}$), 4.06 q J = 7Hz [2] ($OC\underline{H_2}CH_3$) 3.85 s, 3.83 s, 3.81 s and 3.74 s [12] (4xOCH_3), 3.0 d J = 7Hz [2] ($C\underline{H_2}$-CH), 1.18 t, J = 7Hz [3] (CH_3CH_2O).

N-methyl-1,2-bis-(3,4-dimethoxyphenyl)-ethylamine (141)

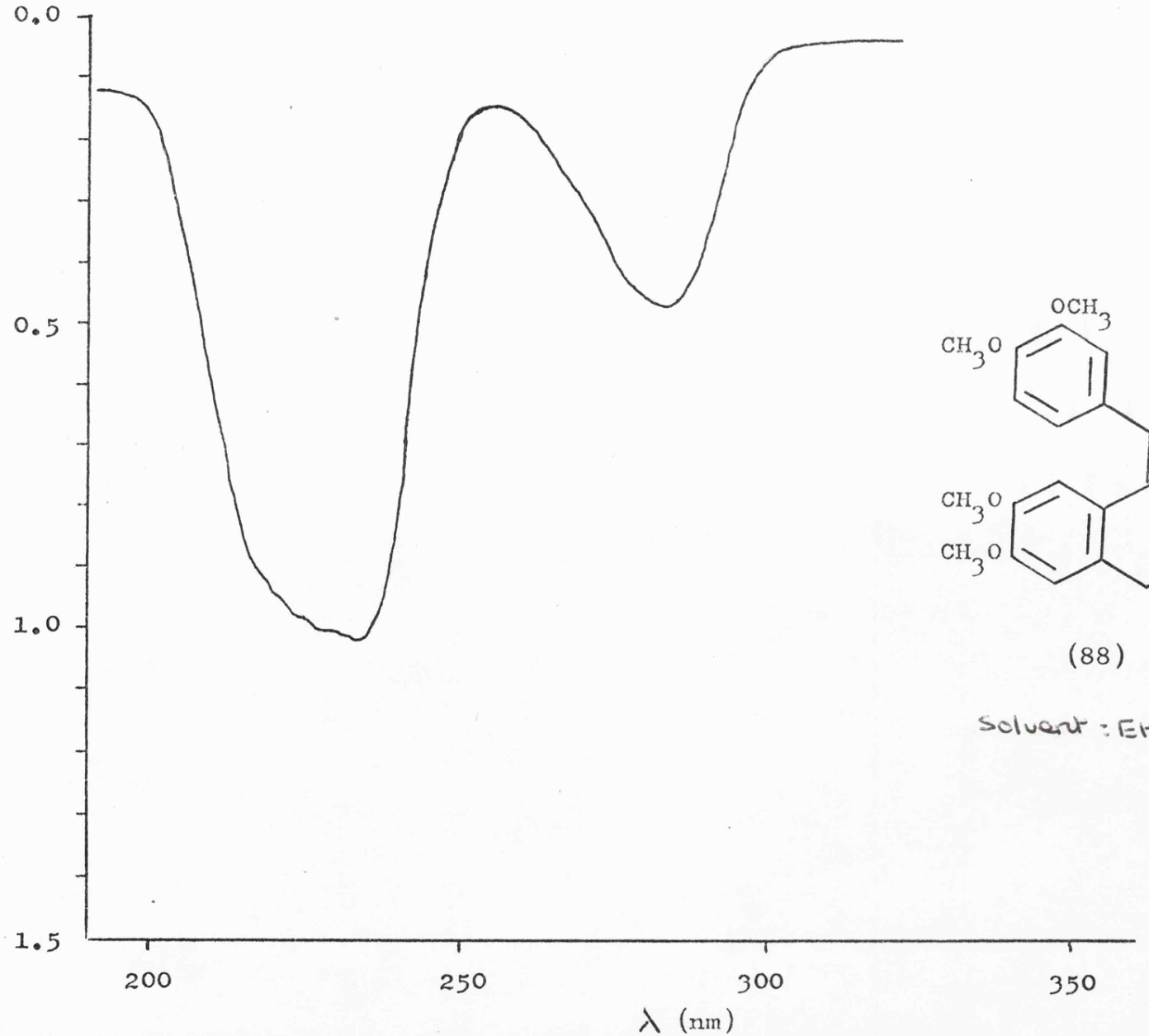
A solution of the preceding carbamate (5g) in dry dioxan (40cm^3) was added dropwise to a stirred suspension of

LAH (3g) in boiling dry dioxan ($150cm^3$) under an atmosphere of dry N_2. After refluxing for 3 hours the mixture was allowed to cool and excess LAH decomposed by adding 20% NaOH ($10cm^3$). After filtration the solvent was removed and the residue treated with 2M NaOH ($50cm^3$) and extracted with Et_2O ($3x50cm^3$). Evaporation of the dried (Na_2SO_4) extracts afforded the required amine as a colourless oil (33%) λ max (ε) 235 (21,500), 280 (9,400). Nmr ($CDCl_3$) 7.0-6.56 complex [6] (Ar-H), 3.86 s, 3.83 s and 3.8 s [12] ($4xOCH_3$), 3.65 m [1] ($\underline{CH}-CH_2$), 2.83 m [2] ($CH-\underline{CH}_2$), 2.22 s [3] ($N-CH_3$), 1.73 broad s [1] removed by D_2O (NH).

Oxidation of N-methyl-1,2-bis-(3,4-dimethoxyphenyl)-ethylamine (141)

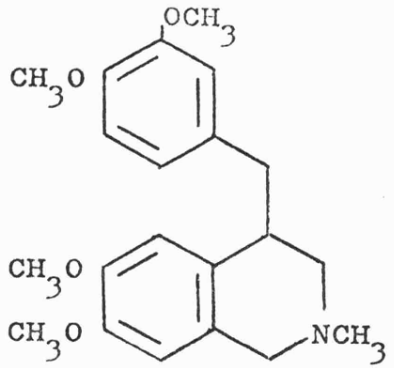
The crude product a brown gum (0.53g) showing UV maxima at 237, 287 and 315 was dissolved in $CHCl_3$ ($5cm^3$) and left to stand at room temperature for several days, whereupon 2,3,6,7-tetramethoxy-9-methylamino-9,10-dihydrophenanthrene (142) crystallised as large colourless prisms (43%). The product was recrystallised from EtOH mp 132-134° λ max (ε) 230 (12,000), 300 broad (9,400). On addition of NaOH λ max (ε) 230 (12,400), 287 (9,100), 318 (9,200). Nmr ($CDCl_3$/DMSO) 7.24 s [1] , 7.22 s [1] , 7.04 s [1] , 6.86 s [1] , (4xAr-H), 4.36 broad [1] ($\underline{CH}-CH_2$), 3.97 s, 3.94 s and 3.89 s [12] ($4xOCH_3$), 3.24 broad [2] ($CH-\underline{CH}_2$), 2.36 s [3] (NCH_3). Mass m/e 330 [16%] , 329 (M^+) [68%] , 328 [11%] , 315 [22%] , 314 [100%] , 300 [16%] , 299 [76%] , 298 [57%] , 278 [19%] , 268 [27%] . High resolution mass gave 329.1624 $C_{19}H_{23}NO_4$ requires 329.1627.

SPECTRA



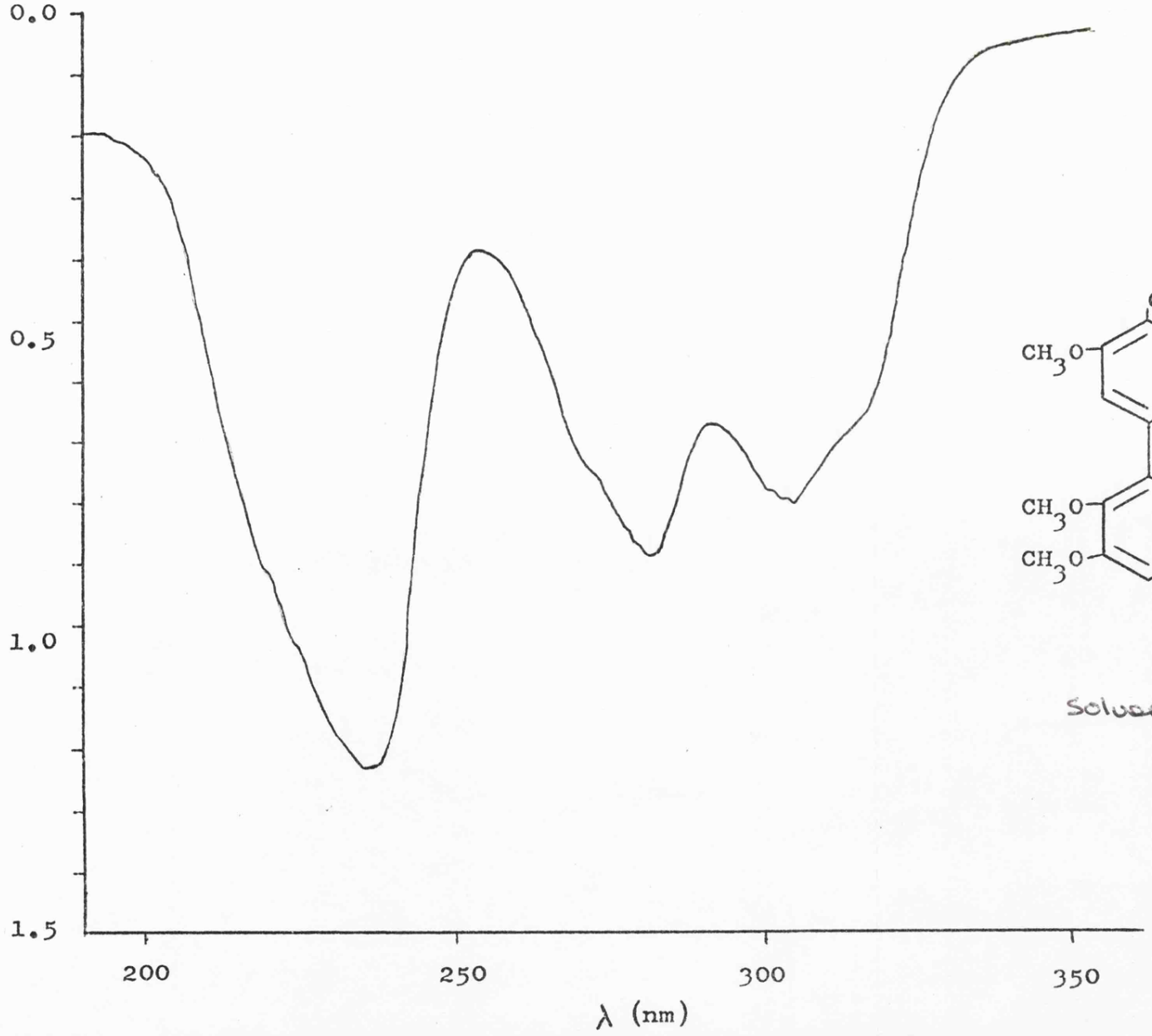
(88)

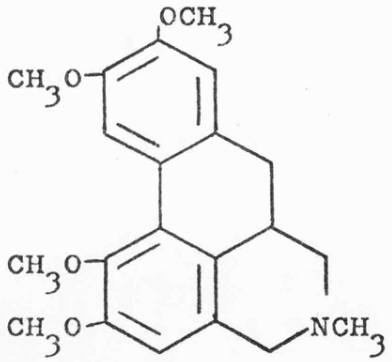
Solvent : EtOH



(88)

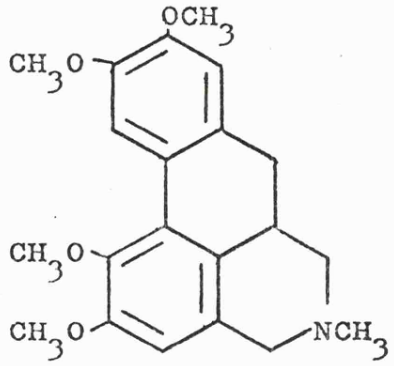
Solvent : $CDCl_3$





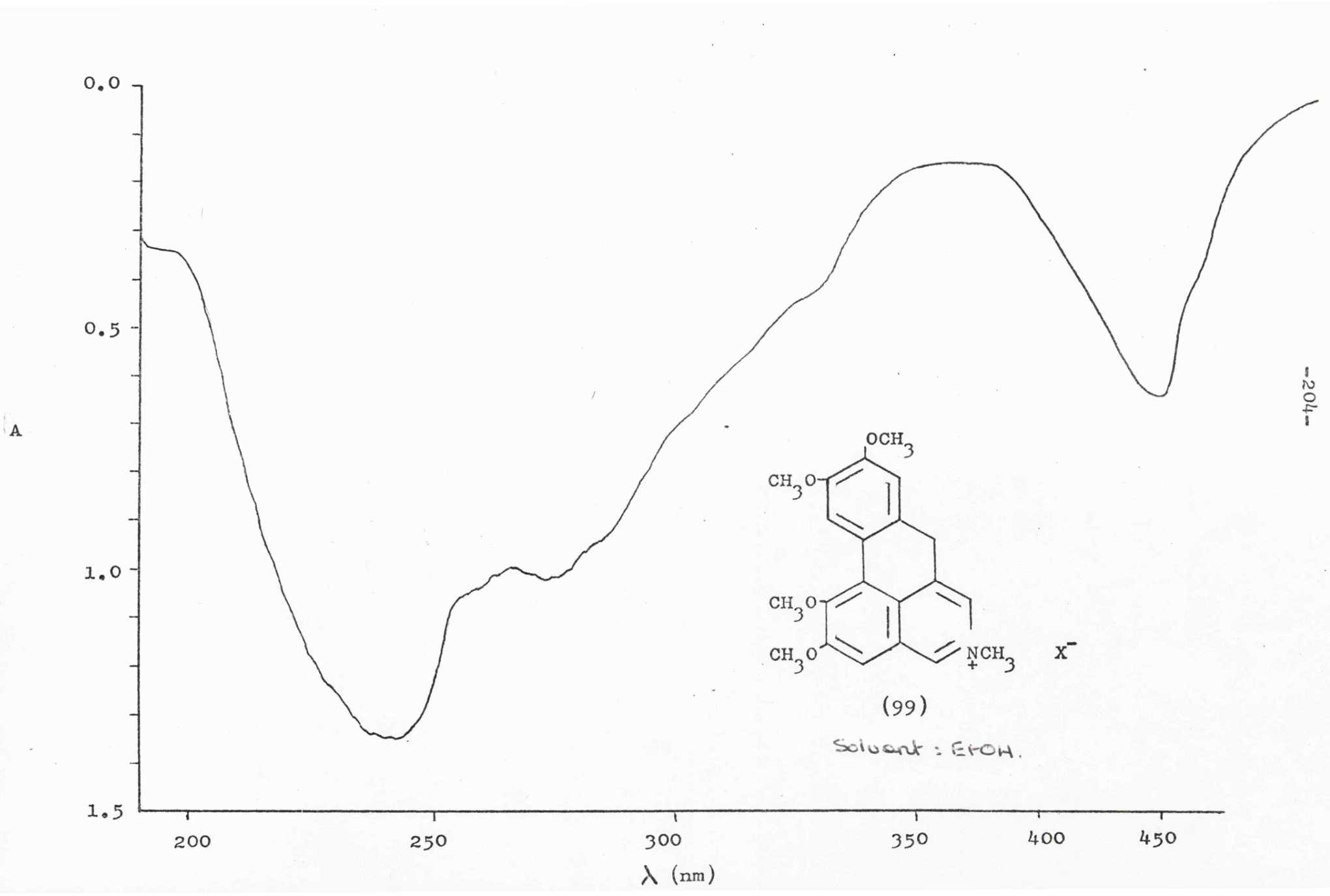
(89)

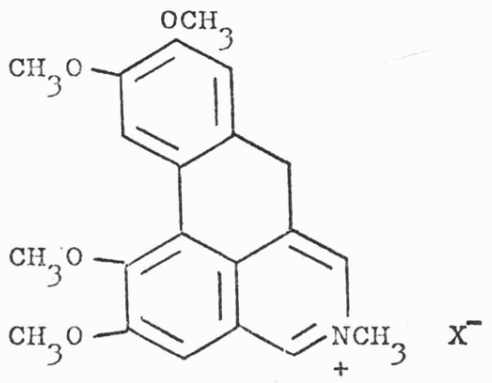
Solvent : EtOH.



(89)

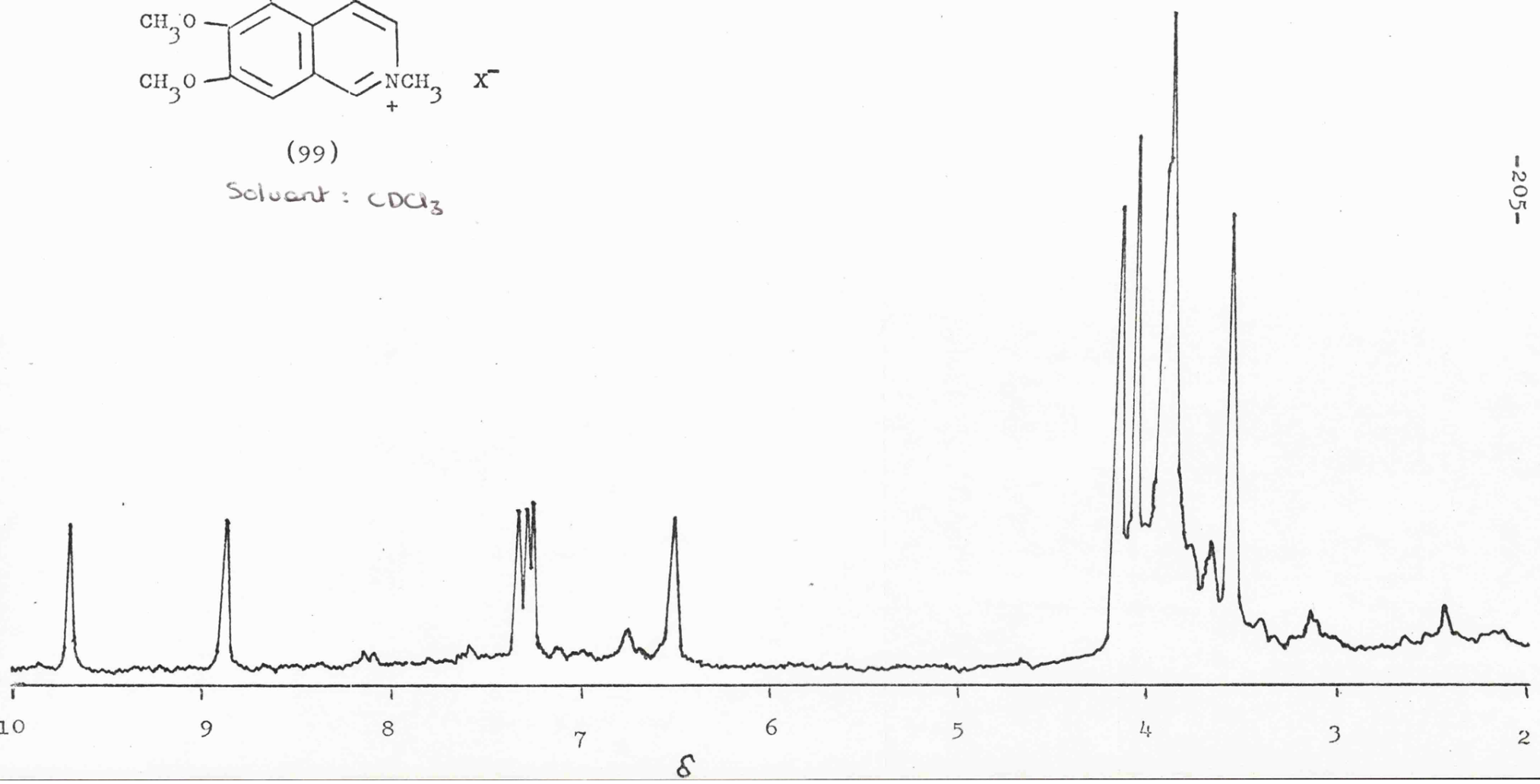
Solvent : $CDCl_3$

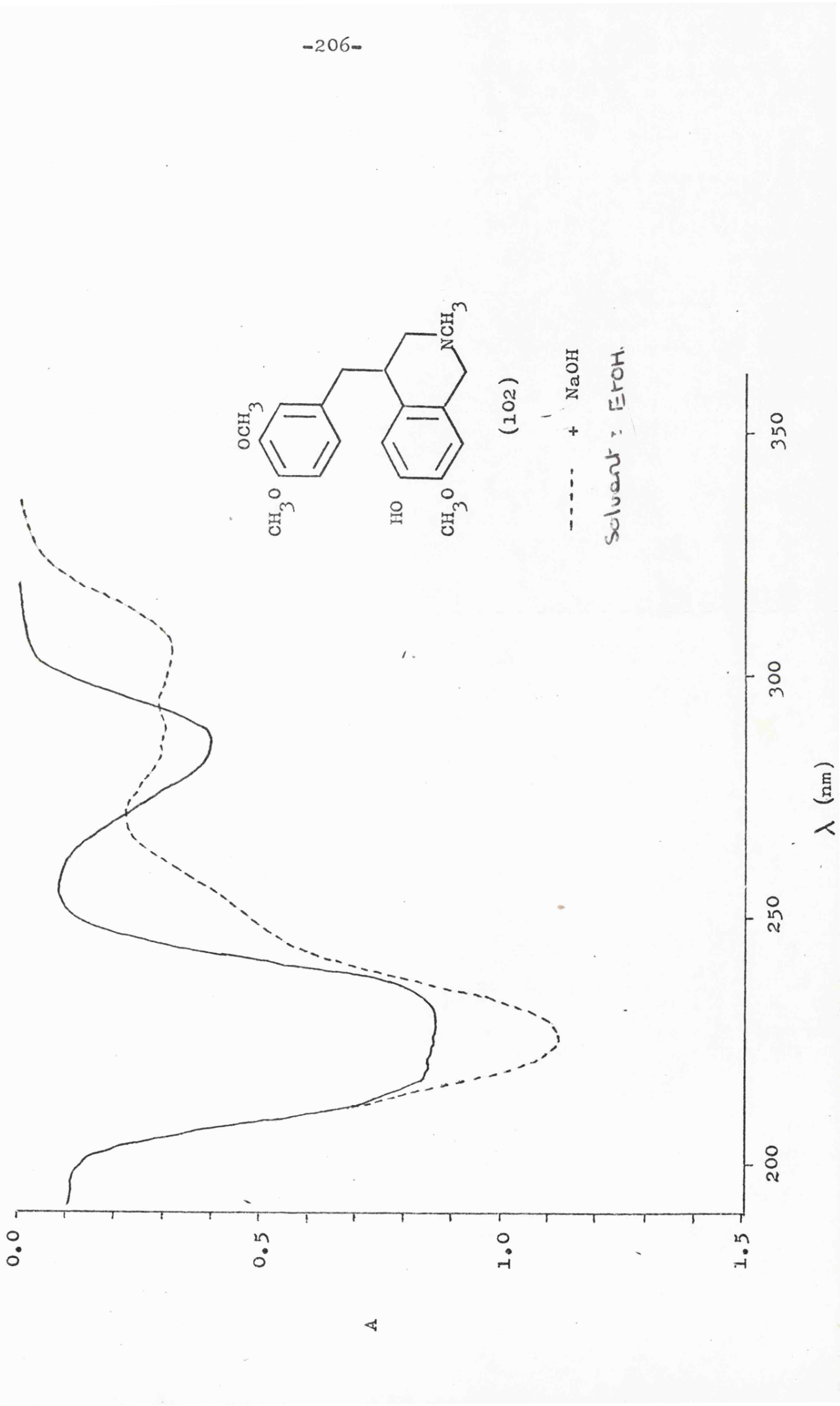

0.0
0.5
1.0
1.5
A
200
250
300
350
400
450
λ (nm)
OCH3
CH3O
CH3O
CH3O
NCH3
X⁻
(99)
Solvent : EtOH.

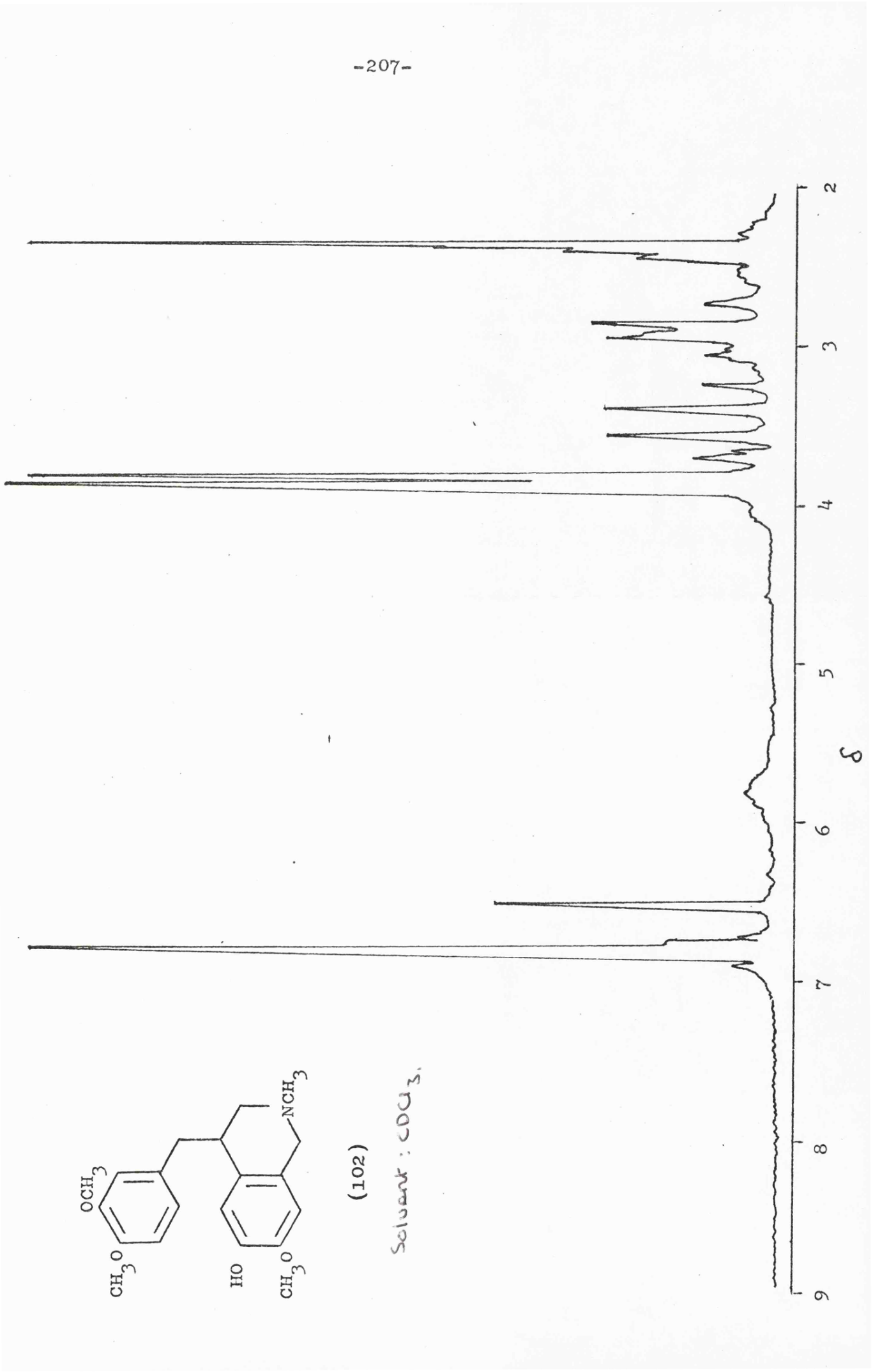


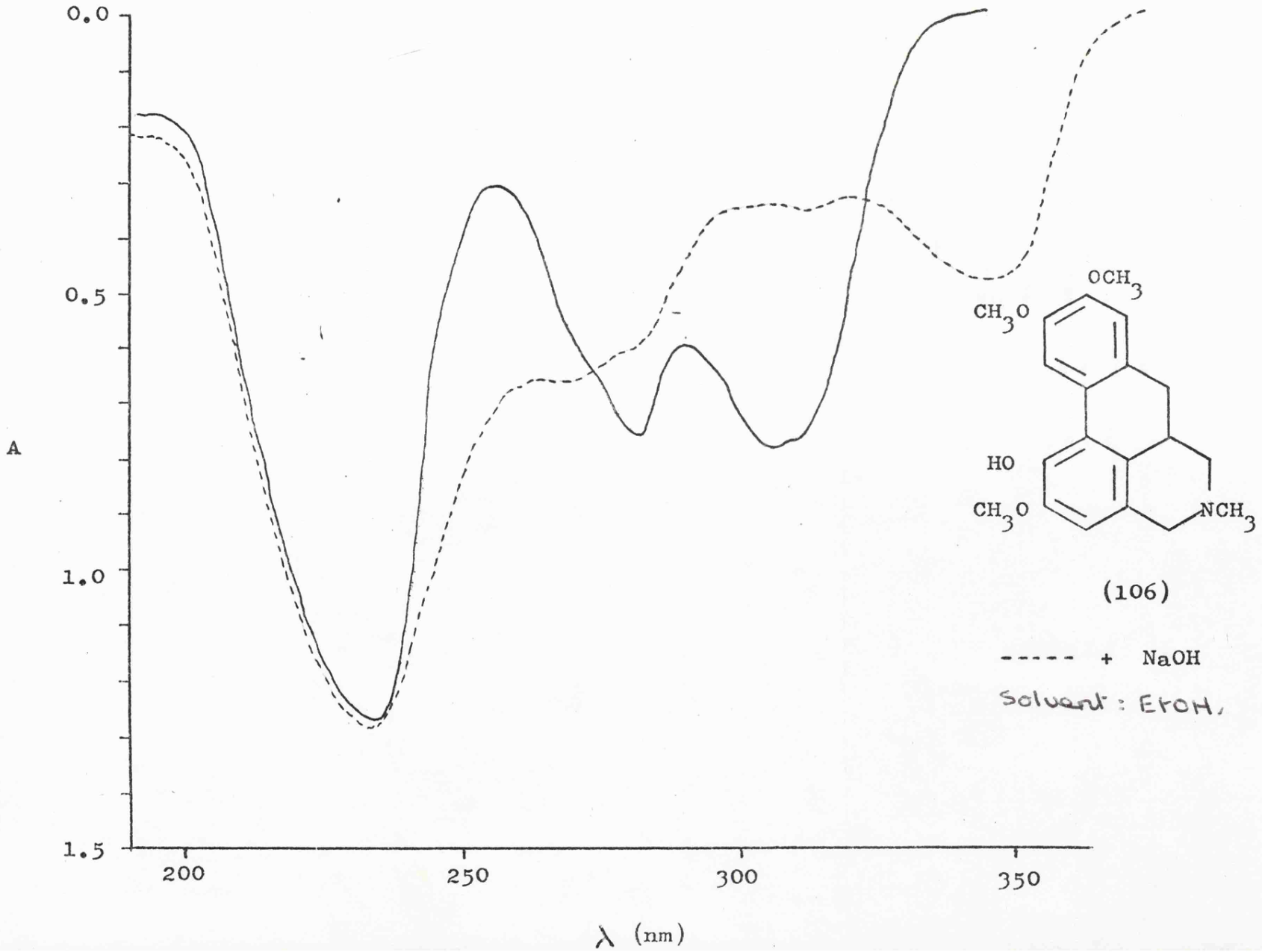
(99)

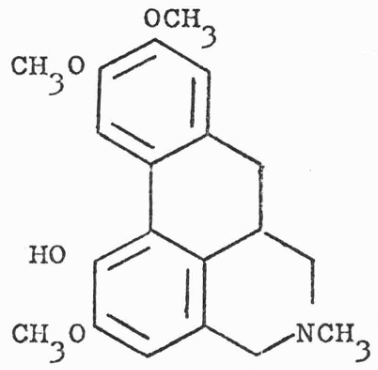
Solvant : $CDCl_3$




0.0
0.5
1.0
1.5
A
200
250
300
350
λ (nm)
OCH3
CH3O
HO
CH3O
NCH3
(102)
----- + NaOH
Solvent : EtOH.

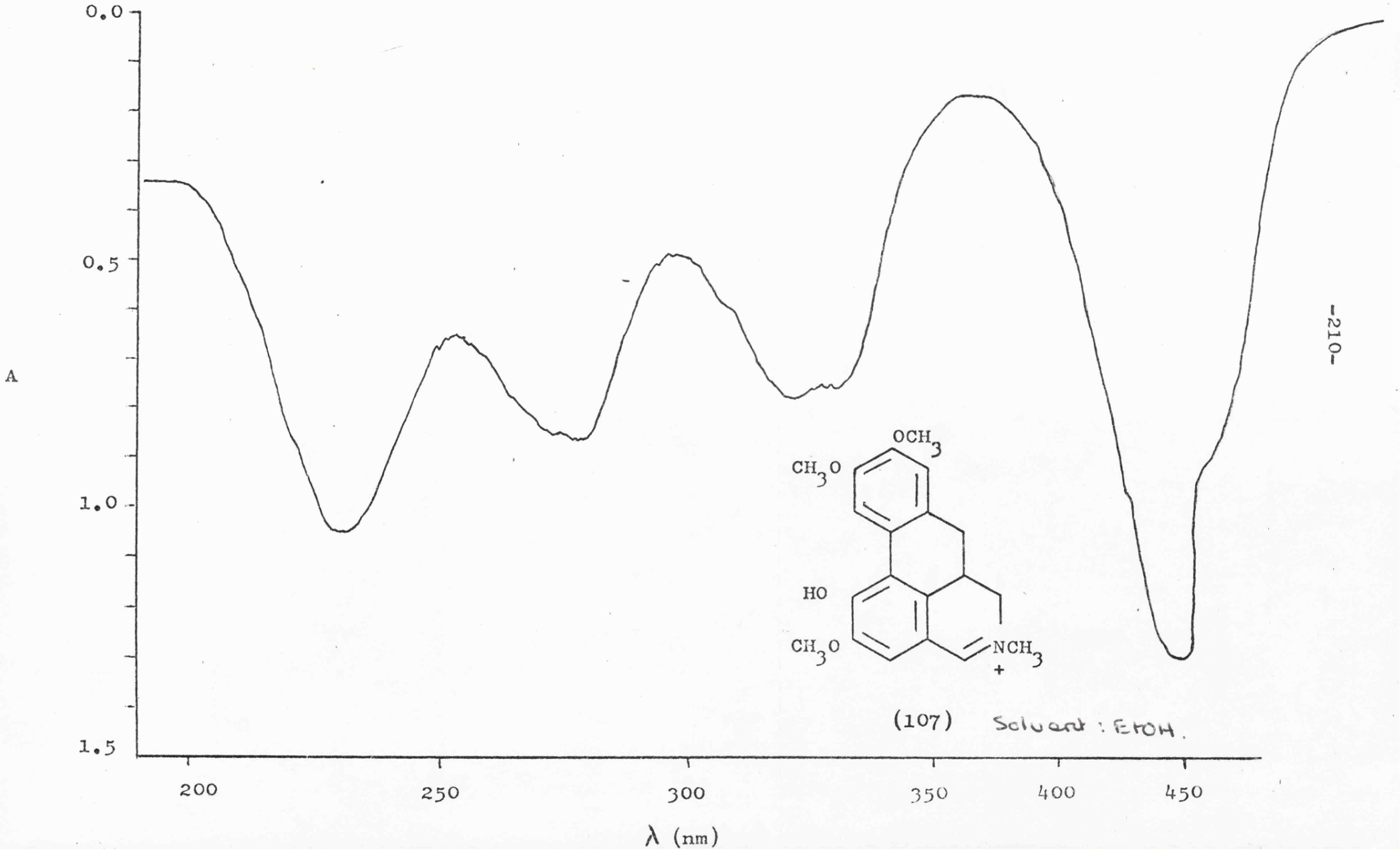

OCH3
CH3O
HO
CH3O
NCH3
(102)
Solvent : CDCl3.
9
8
7
6
5
4
3
2
δ


0.0
0.5
1.0
1.5
A
200
250
300
350
λ (nm)
OCH3
CH3O
HO
CH3O
NCH3
(106)
----- + NaOH
Solvant : EtOH.

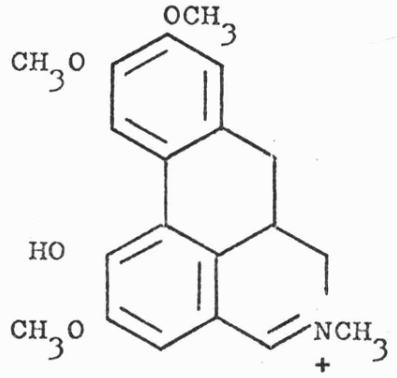


(106)

Solvent : $CDCl_3$

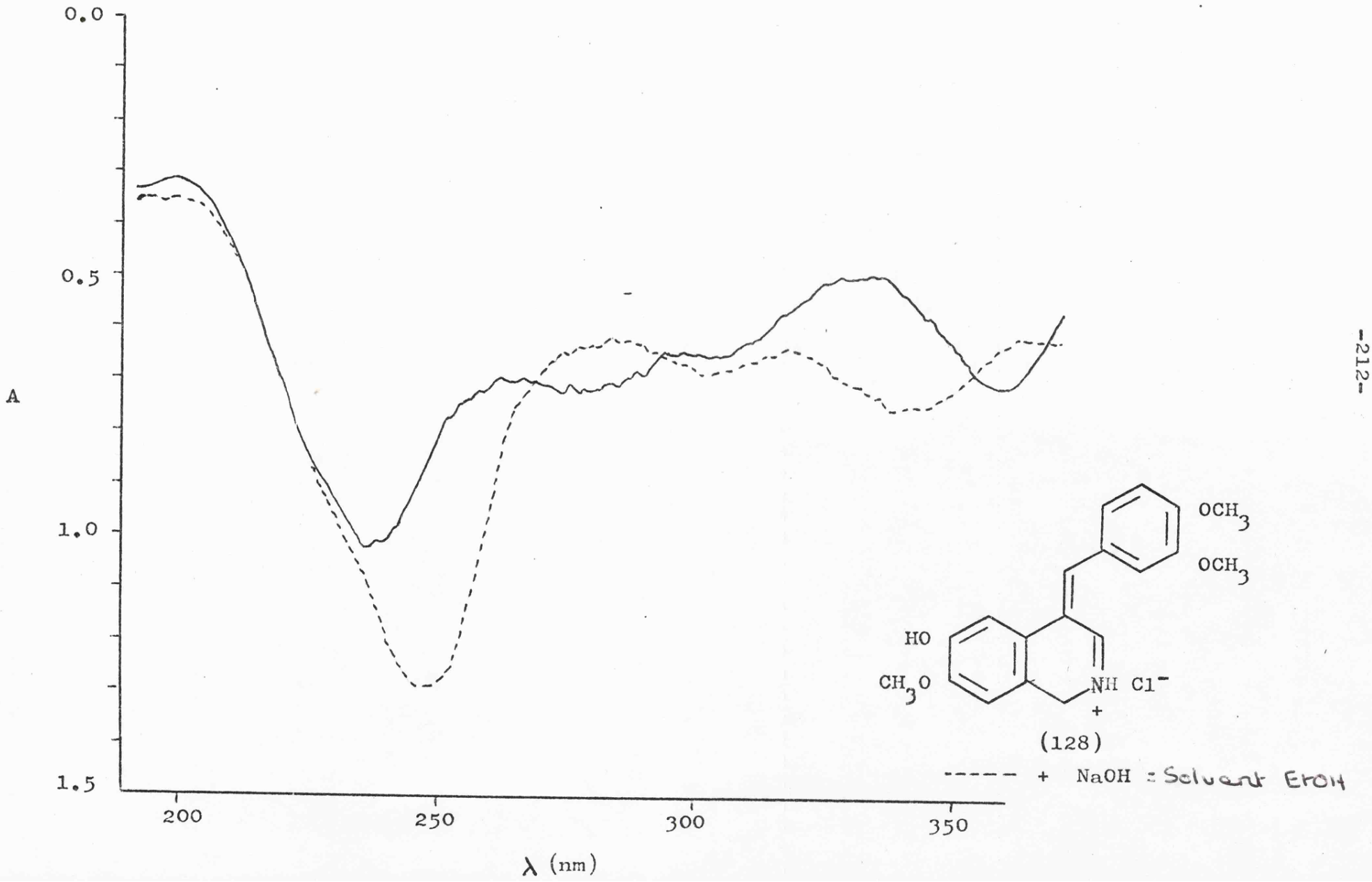


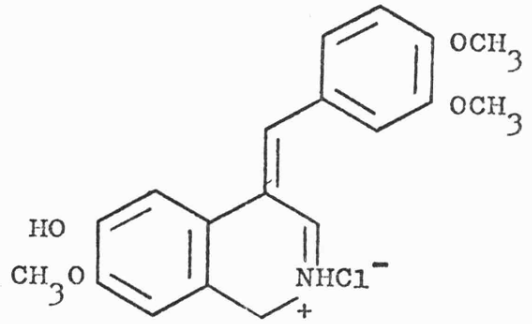
(107) Solvent : EtOH.



(107)

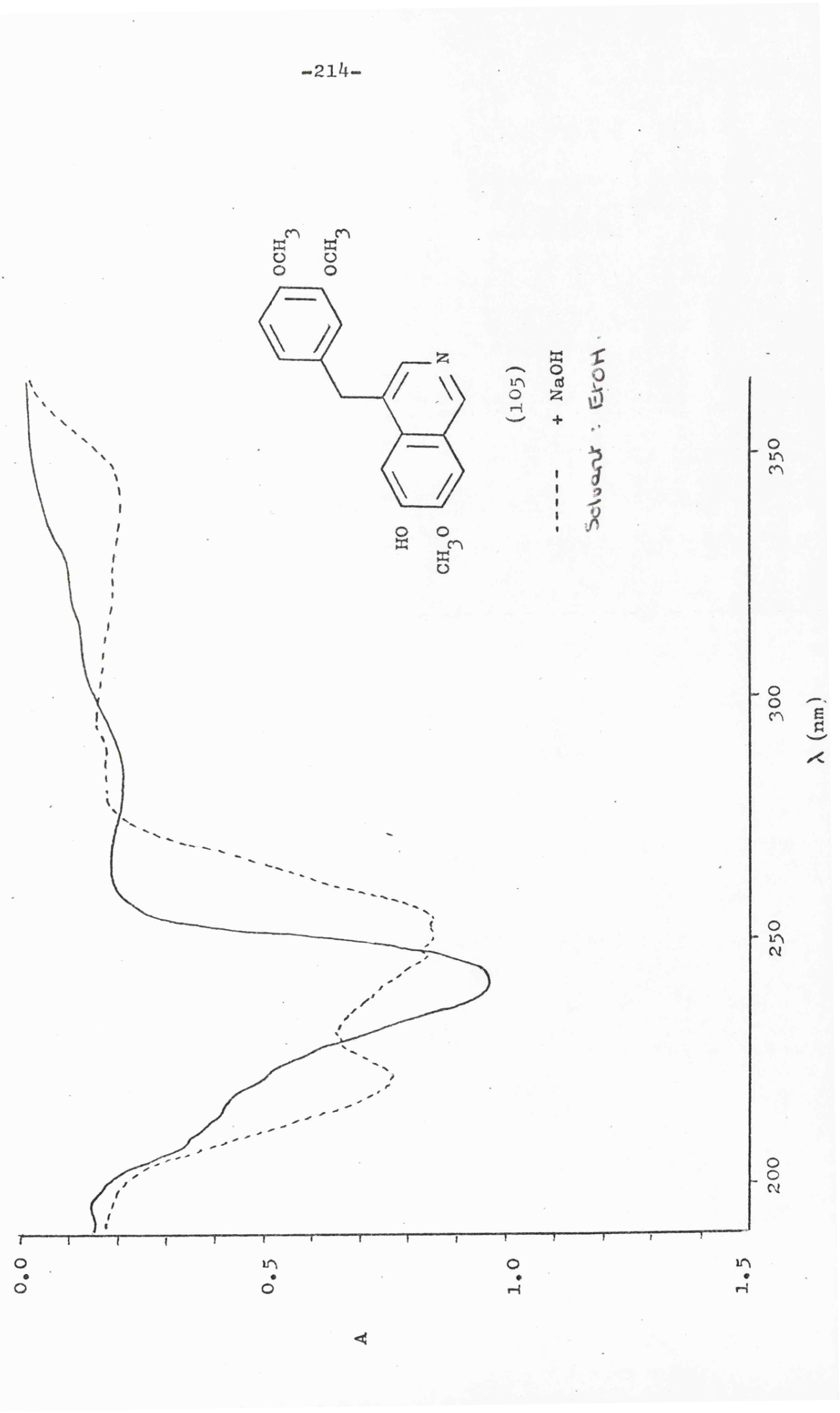
Solvent : $CDCl_3$

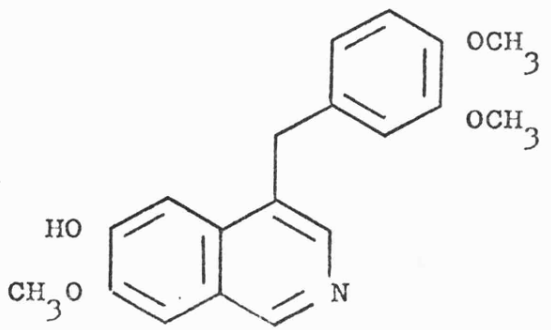

0.0
0.5
1.0
1.5
A
200
250
300
350
λ (nm)
OCH3
OCH3
HO
CH3O
NH Cl⁻
+
(128)
----- + NaOH : Solvent EtOH



(128)

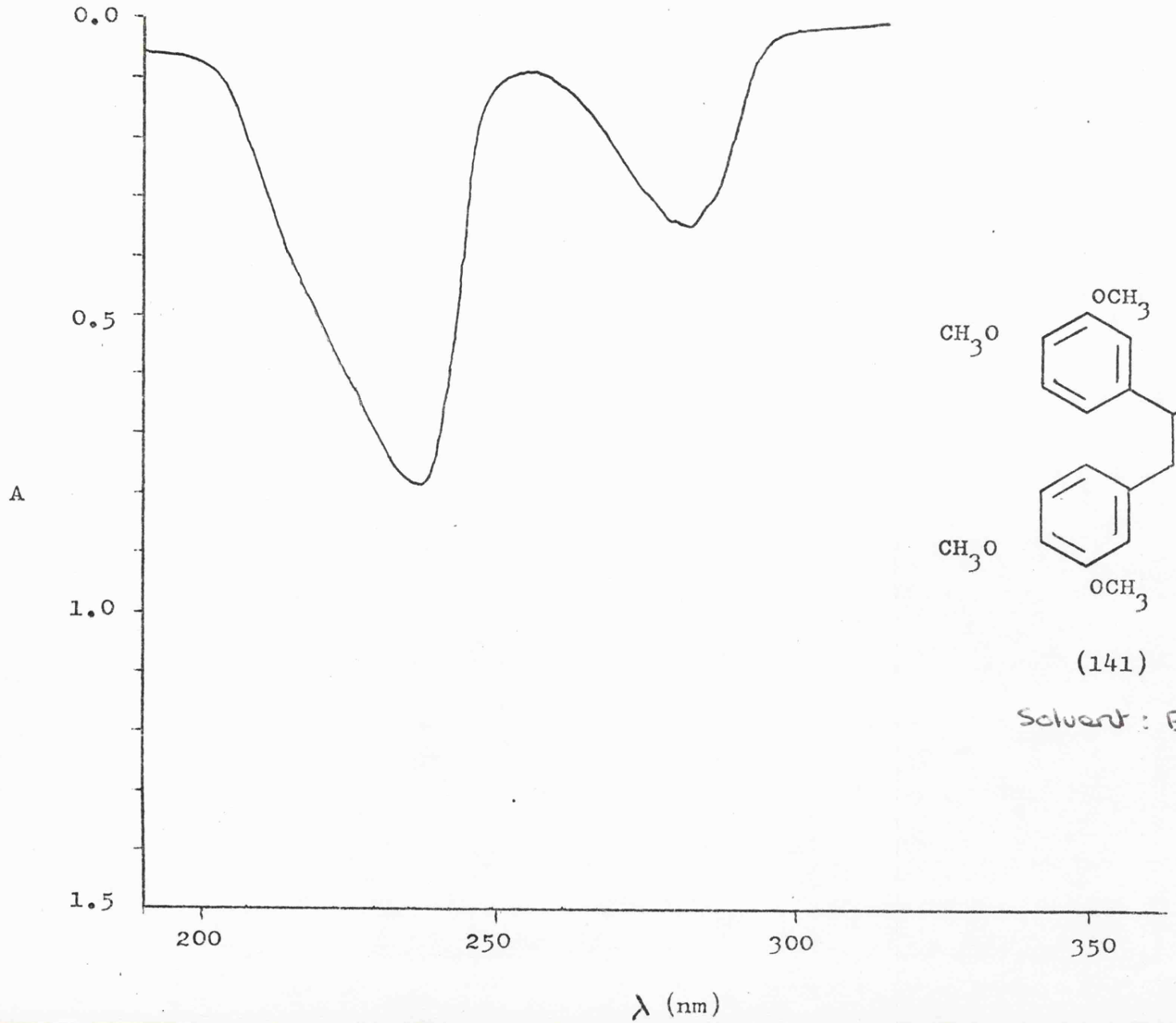
Solvent : TFA


OCH3
OCH3
N
HO
CH3O
(105)
+ NaOH
Solvent : EtOH
A
0.0
0.5
1.0
1.5
200
250
300
350
λ (nm)



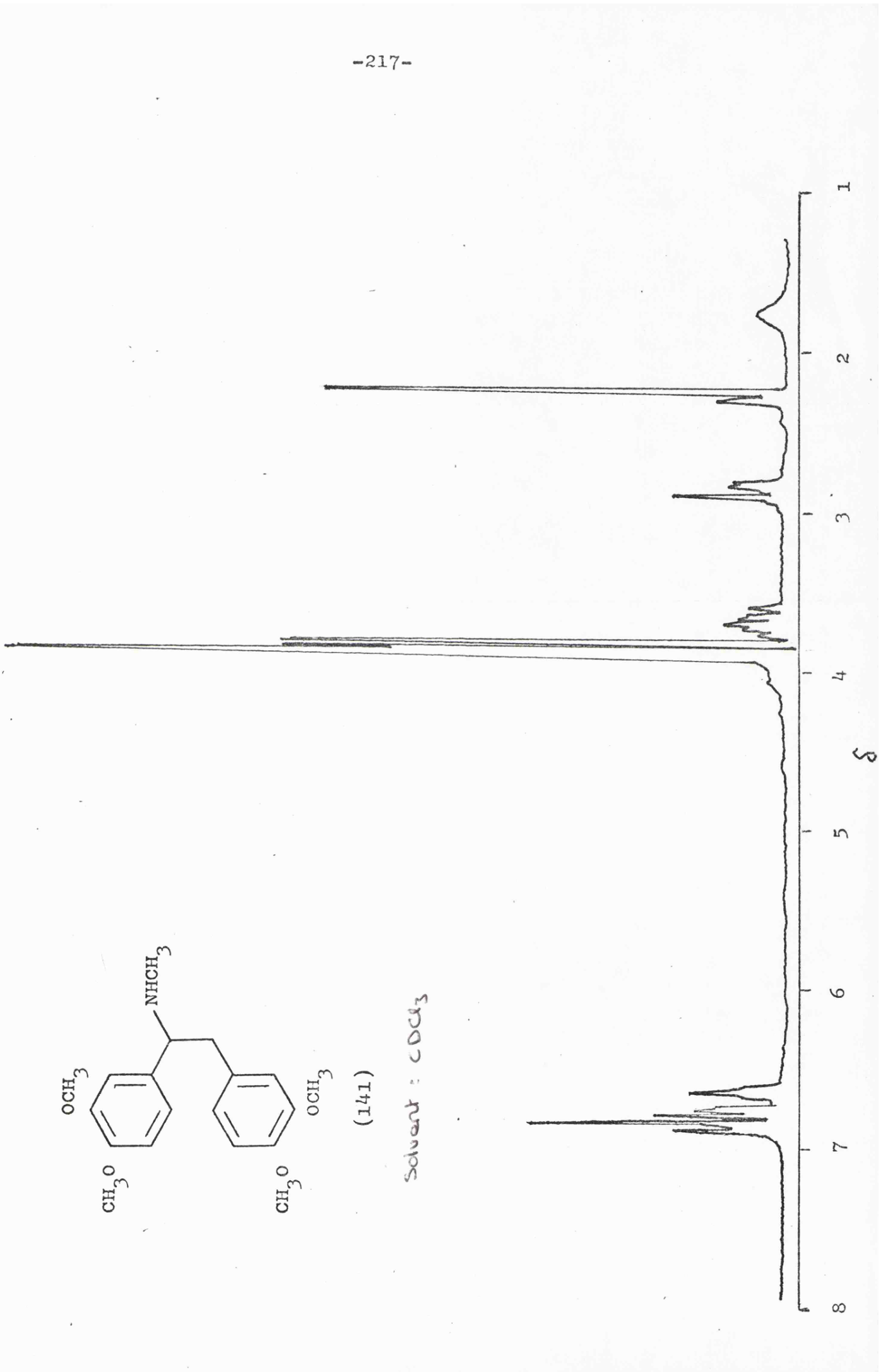
(105)

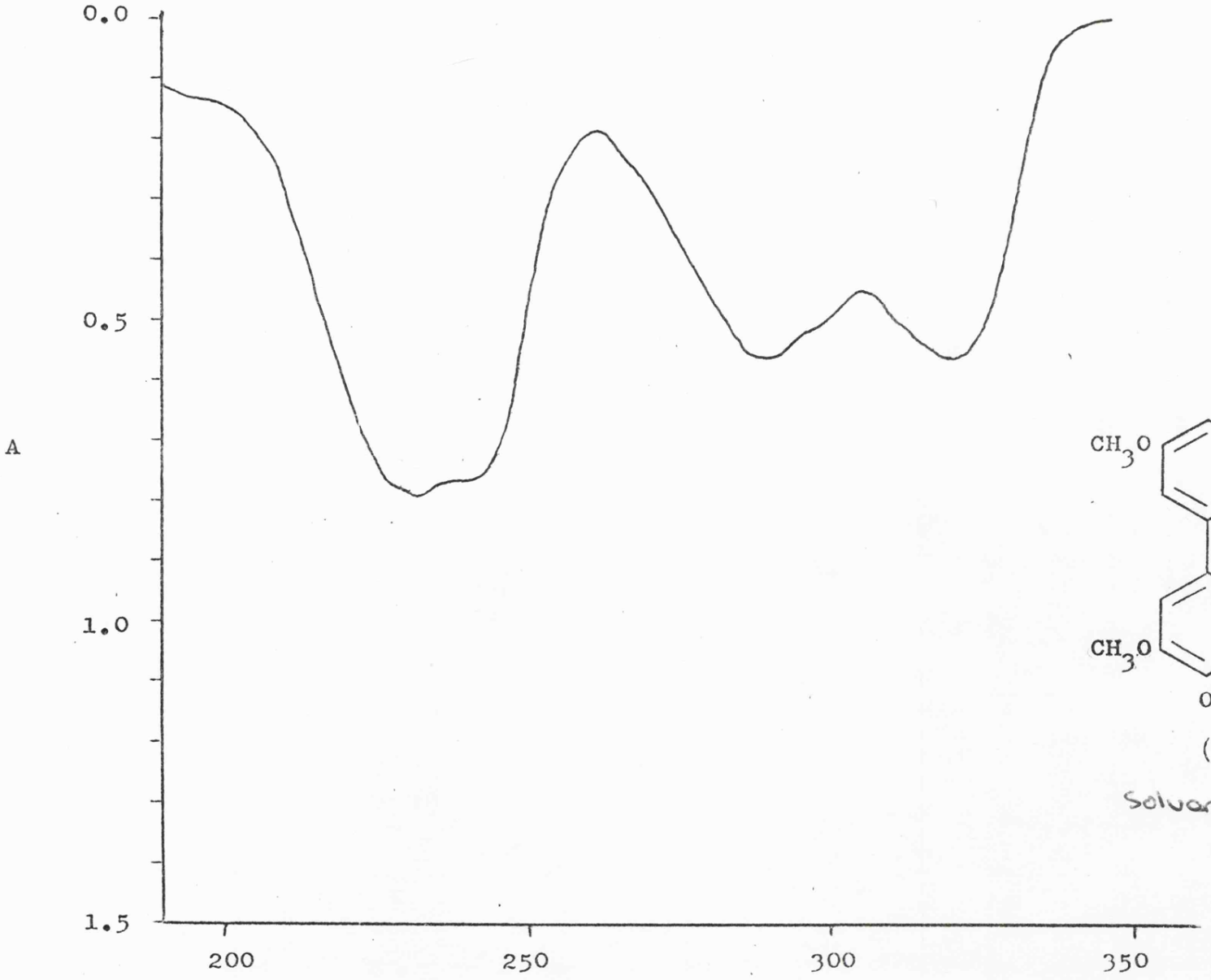
solvent : $CDCl_3$

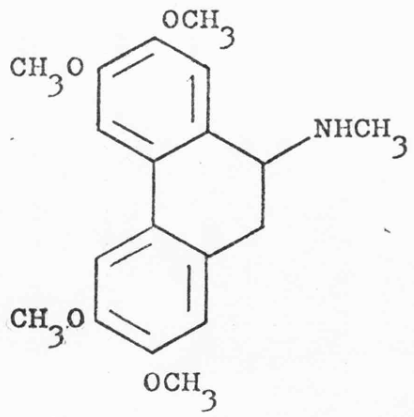


(141)

Solvent : EtOH.

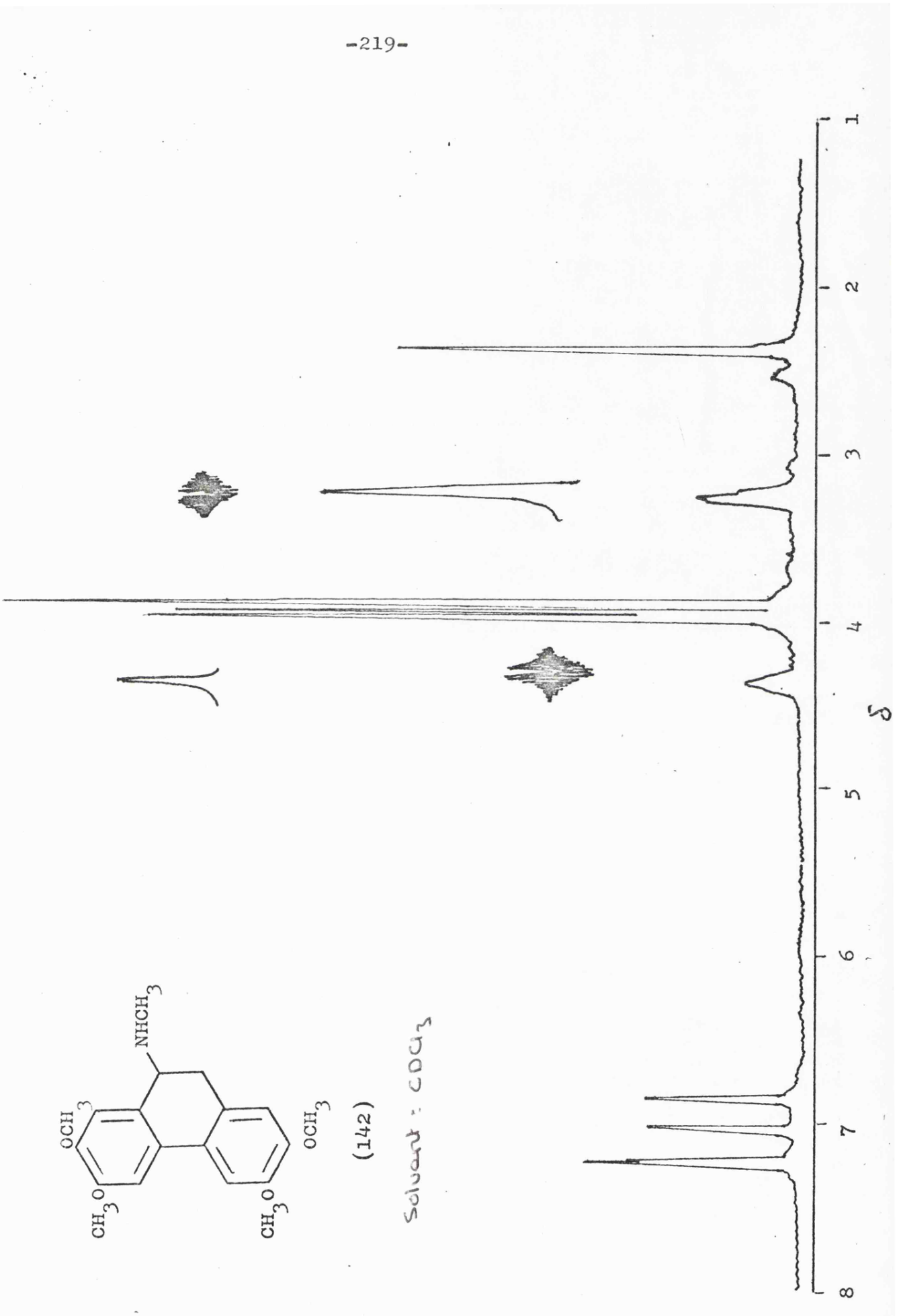

NHCH3
OCH3
CH3O
CH3O
OCH3
(141)
Solvent : CDCl3
8
7
6
5
4
3
2
1
δ

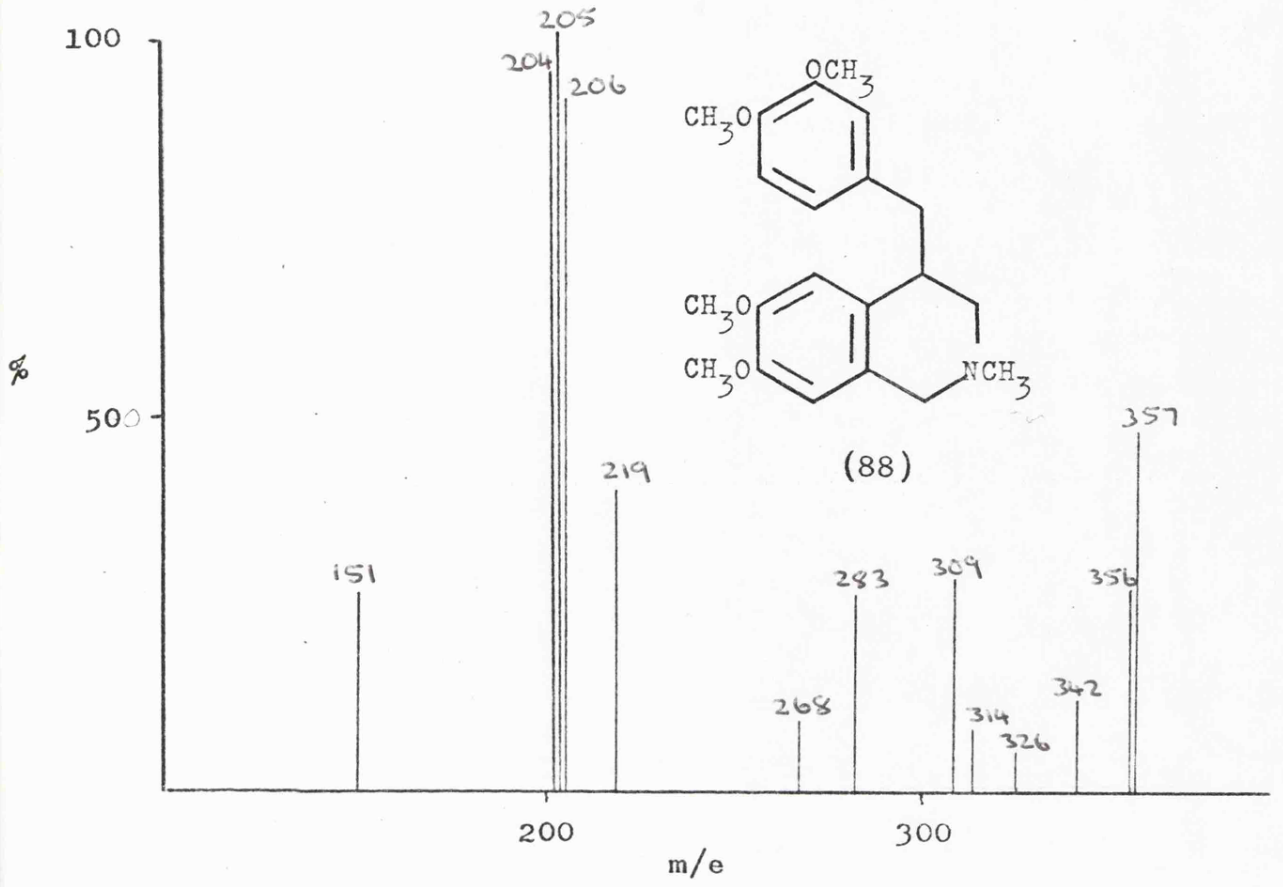




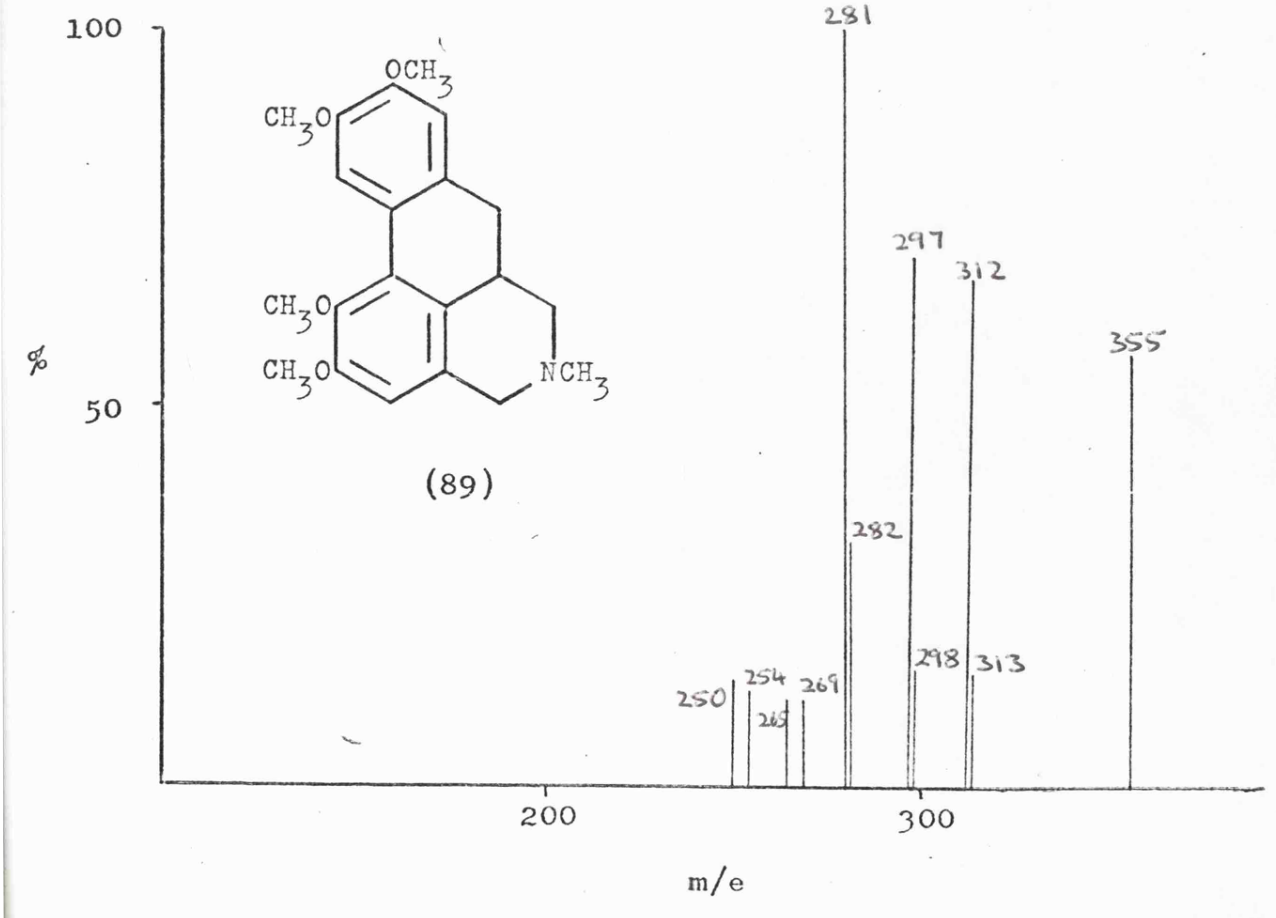
(142)

Solvent : EtOH.

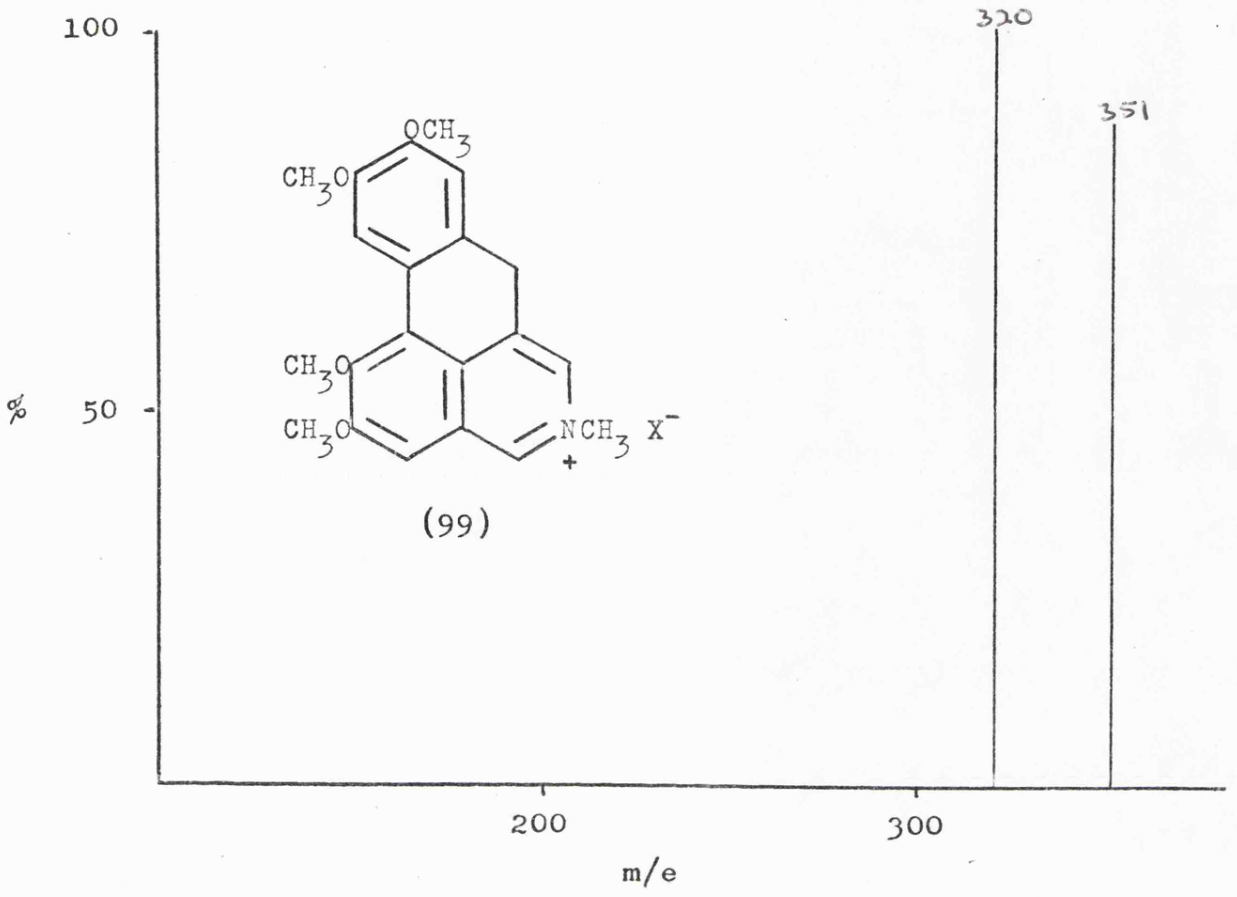

NHCH3
OCH3
CH3O
CH3O
OCH3
(142)
Solvent : CDCl3
1
2
3
4
5
6
7
8
δ


100
50
%
205
204
206
219
151
283
309
268
314
326
342
356
357
200
300
m/e
OCH3
CH3O
CH3O
CH3O
NCH3

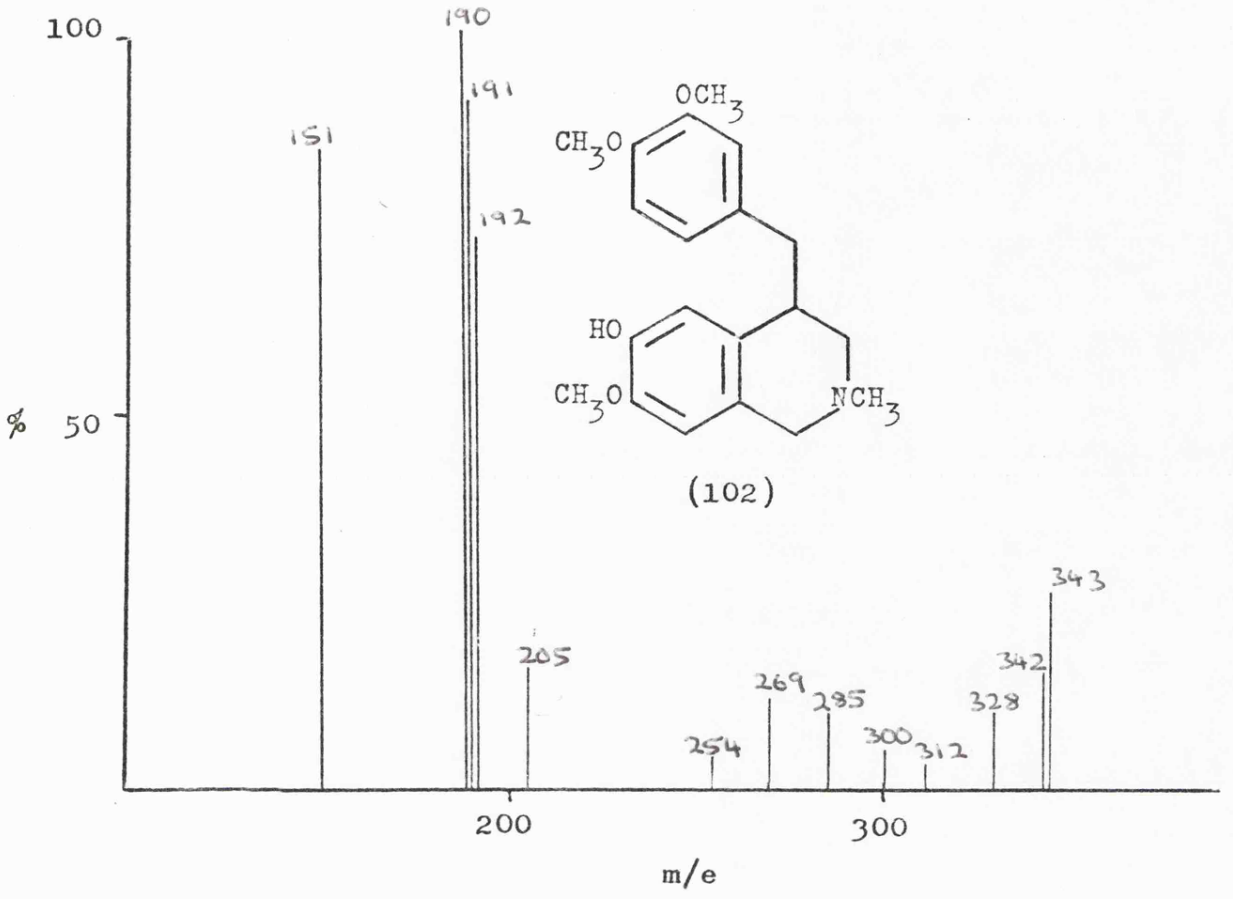
(88)


100
50
%
281
297
312
355
282
298
313
250
254
265
269
200
300
m/e
OCH3
CH3O
CH3O
CH3O
NCH3

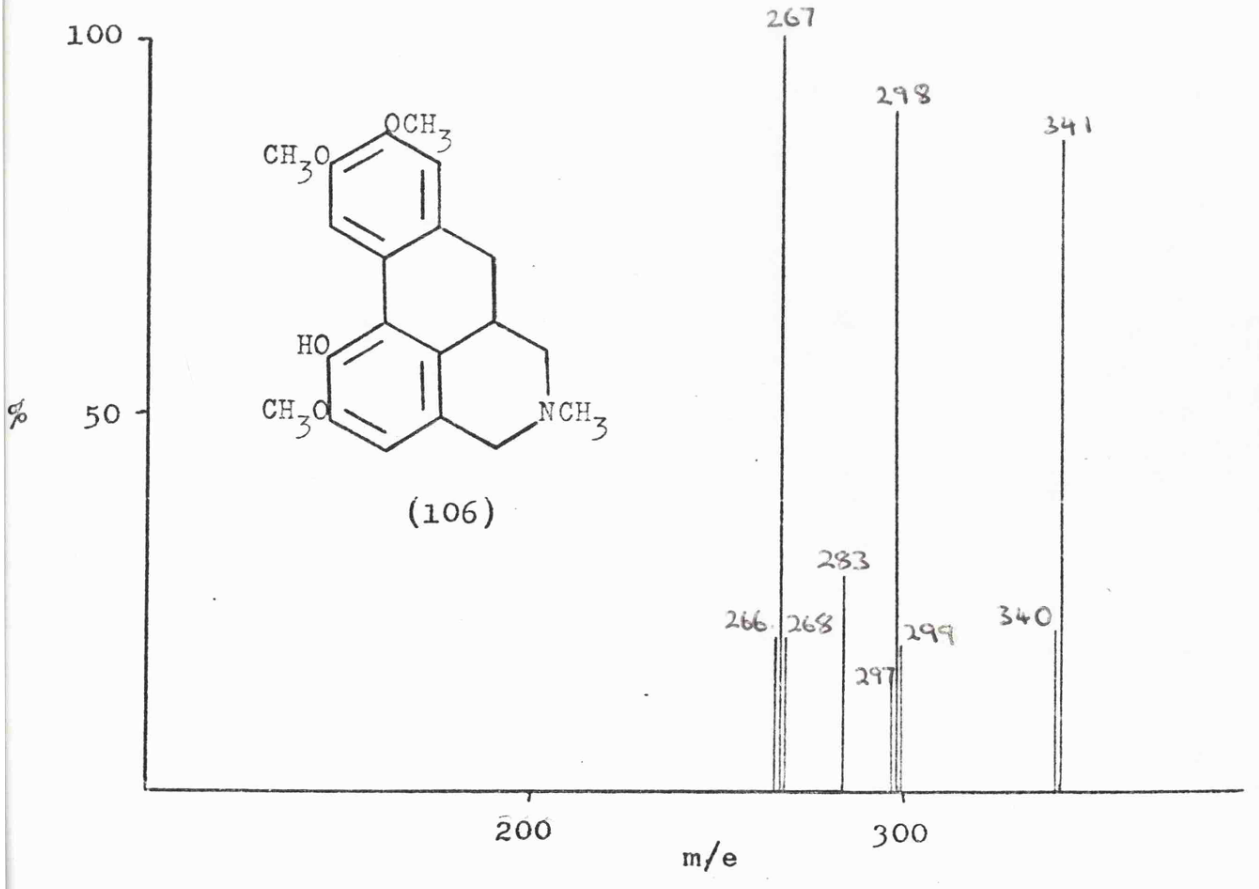
(89)



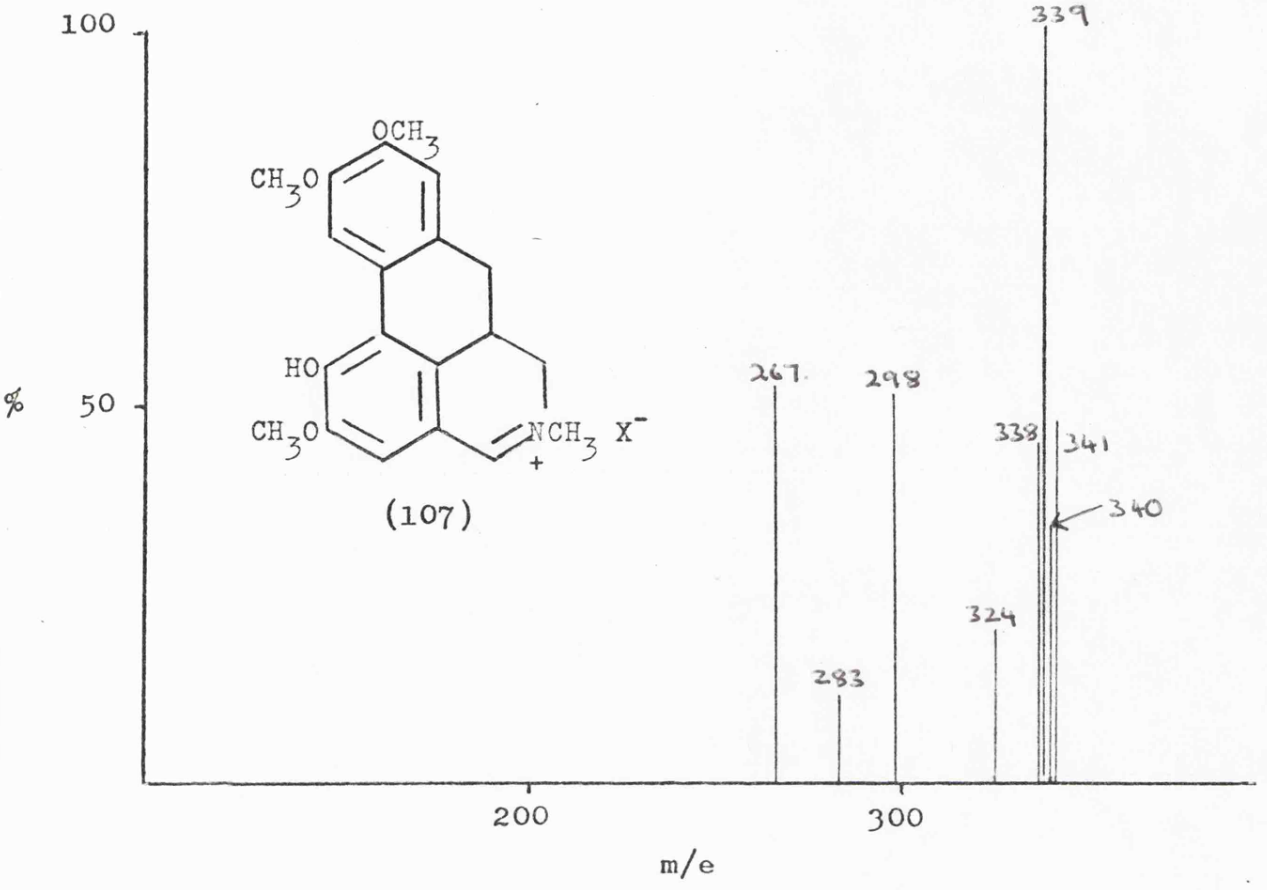
(99)


100
%
50
190
191
192
151
205
254
269
285
300
312
328
342
343
200
300
m/e
OCH3
CH3O
HO
CH3O
NCH3

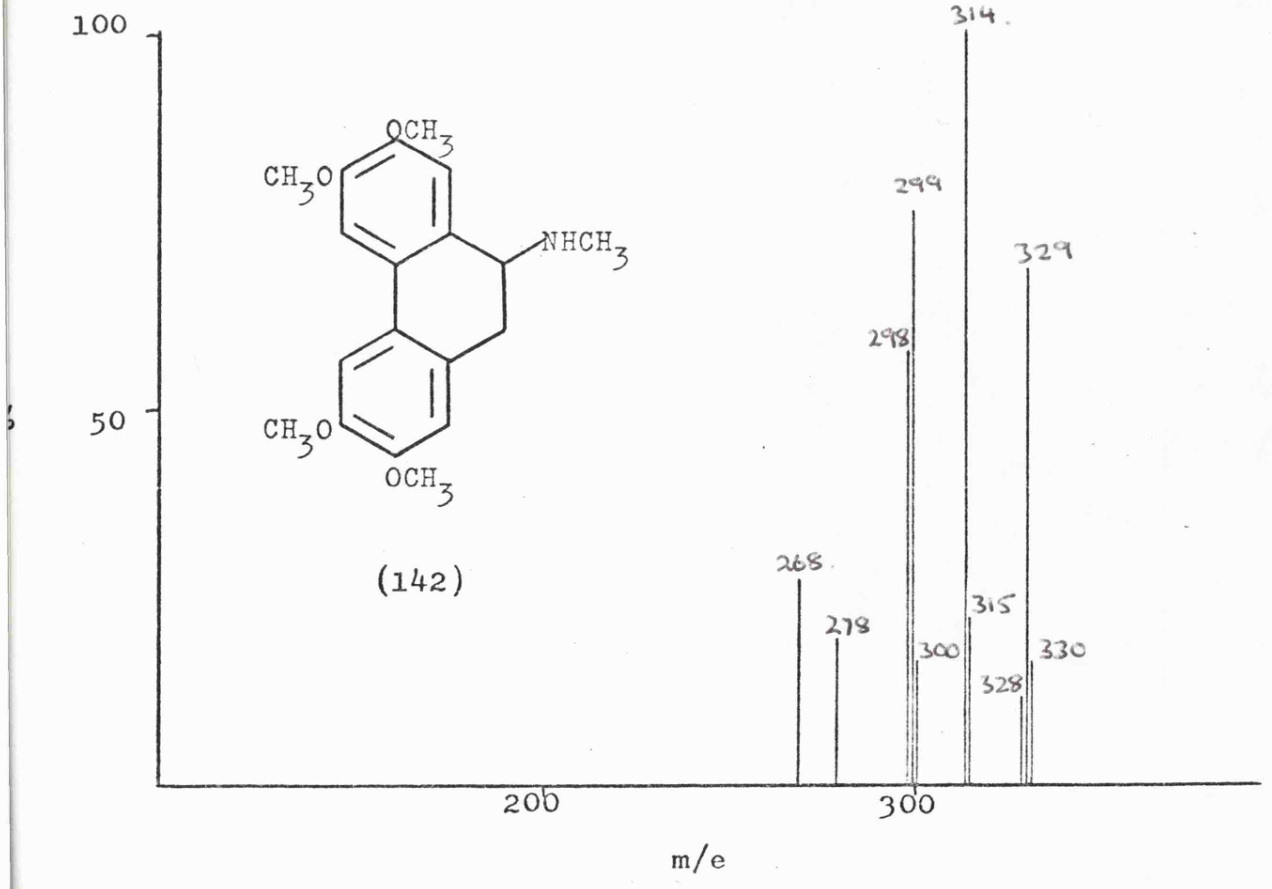
(102)


100
%
50
267
298
341
266
268
283
297
299
340
200
300
m/e
OCH3
CH3O
HO
CH3O
NCH3

(106)


100
50
%
339
267
298
338
341
340
324
283
200
300
m/e
OCH3
CH3O
HO
CH3O
NCH3 X-
+

(107)


100
50
314
299
329
298
268
278
315
300
330
328
200
300
m/e
OCH3
CH3O
NHCH3
CH3O
OCH3

(142)

REFERENCES

1. W.I. Taylor and A.R. Battersby, Ed., "Oxidative Coupling of Phenols", Marcel Dekker, New York, N.Y., 1967

2. T. Kametani and K. Fukumoto, Synthesis 657 (1972)

3. M. Shamma, "The Isoquinoline Alkaloids", Academic Press, New York, N.Y., 1972

4. M.N. Afzaz, A.D. Allbutt, A. Jordan and G.W. Kirby, Chem. Commun., 996 (1969)

5. A. Ronlan, O. Hammerich and V.D. Parker, J. Am. Chem. Soc., 95, 7132 (1973); V.D. Parker and A. Ronlan ibid 97, 4714 (1975), A. Ronlan, K. Bechgaard and V.D. Parker, Acta. Chem. Scand., 27, 2375 (1973)

6. M. Sainsbury and R.F. Schinazi, Chem. Commun., 718 (1972), M. Sainsbury and J. Wyatt, J. Chem. Soc., Perkin Trans., 1, 661 (1976); U. Palmquist, A. Nilsson, V.D. Parker and A. Ronlan, J. Am Chem. Soc., 98, 2571 (1976)

7. J.R. Falck, L.L. Miller and F.R. Stermitz, J. Am. Chem. Soc., 96, 2981 (1974)

8. L.L. Miller, F.R. Stermitz and J.R. Falck, J. Am Chem. Soc., 93, 5941 (1971), ibid 95, 2651 (1973), J.R. Falck, L.L. Miller and F.R. Stermitz, Tetrahedron, 30, 931 (1974). E. Kotani and S. Tobinaga, Tetrahedron Letters, 4759 (1973)

9. M.A. Schwartz, B.F. Rose and B. Vishnuvajjala, J. Am. Chem. Soc., 95, 612 (1973)

10. S.M. Kupchan and A.J. Liepa, J. Am. Chem. Soc., 95, 612 (1973)

11. S.M. Kupchan, A.J. Liepa, V. Kameswaran and R.F. Bryan,

J. Am. Chem. Soc., 95, 6861 (1973)

12. S.M. Kupchan, V. Kameswaran, J.T. Lynn, D.K. Williams and A.J. Liepa, J. Am. Chem. Soc., 97, 8622 (1975)

13. T. Kametani, R. Charubala, M. Ihara, M. Koizumi, K. Takabashi and K. Fukumoto, J. Chem. Soc. C., 3315 (1971), T. Kametani, K. Takabashi, T. Houda, M. Ihara and K. Fukumoto, Chem. Pharm. Bull. 20, 1793 (1972)

14. S.M. Kupchan and C.K. Kim, J. Am. Chem. Soc., 97, 5623 (1975)

15. S.M. Kupchan, O.P. Dhingra, C.K. Kim and V. Kameswaran, J. Org. Chem., 41, 4047 (1976)

16. S.M. Kupchan, O.P. Dhingra and C.K. Kim ibid, 41, 4049 (1976)

17. I.W. Elliot J. Org. Chem. 42, 1090 (1977)

18. M.A. Schwartz, B.F. Rose, R.A. Holton, S.W. Scott and B. Vishnuvajjala, J. Am. Chem. Soc., 99, 2571 (1977)

19. M.S. Bains, J.C. Arthur Jr., and O. Hinojosa, J. Am. Chem. Soc., 91, (1969)

20. T. Kametani, M. Ihara, M. Takernura, Y. Satoh, H. Terasawa, Y. Ohta, K. Fukumoto and K. Takahashi, J. Am. Chem. Soc., 99, 3805 (1977)

21. A. McKillop, A.G. Turrell and E.C. Taylor, J. Org. Chem., 42, 764 (1977)

22. E.C. Taylor, J.G. Andrade and A. McKillop, Chem. Commun., 538 (1977)

23. J. Hartenstein and G. Satzinger, Angew. Chem. Int. Ed. Engl. 16 730 (1977)

24. J.M. Bobbit, D.P. Winters and J.M. Kiely, J. Org. Chem., 30, 2459 (1965)

25. R. Pschorr, Ber. 39, 3106 (1906)

26. J.W. Cook, G.T. Dickinson, D.E. Ellis and J.D. Louden, J. Chem. Soc., 1074 (1949)

27. S.F. Dyke, M. Sainsbury, D.W. Brown and M.N. Palfreyman Tetrahedron 25, 5365 (1969)

28. B.Y. Riad MSc Thesis University of Bath 1972.

29. M. von Milbearbeitet and M. Silberbach, Ber. 37, 1926 (1904)

30. B.H. Bhide and S.F. Dyke unpublished work.

31. S.M. Kupchan and R.M. Konojia, Tetrahedron Letters 5353 (1966)

32. N.C. Yang, G.R. Lenz and A. Shani, Tetrahedron Letters 2941 (1966)

33. M.P. Cava, S.C. Havlicek, A. Lindert and R.J. Spangler, Tetrahedron Letters 2937 (1966)

34. S.F. Dyke and M. Sainsbury, Tetrahedron 23, 3161 (1967)

35. W.D.G. Lugton, PhD Thesis, University of Bath (1969).

36. Privat Communication from A.J. Liepa.

37. W.H. Baarschers, R.R. Arndt, K. Pachler, J.A. Weisbach and B. Douglas, J. Chem. Soc., 4778 (1964)

38. F.L. Pyman, J. Chem. Soc., 1610 (1909)

39. R.F. Borch, M.D. Bernstein and H.D. Durst, J. Am. Chem. Soc., 93, 2897 (1975)

40. G.N. Walker, J. Am. Chem. Soc., 76, 3999 (1954)